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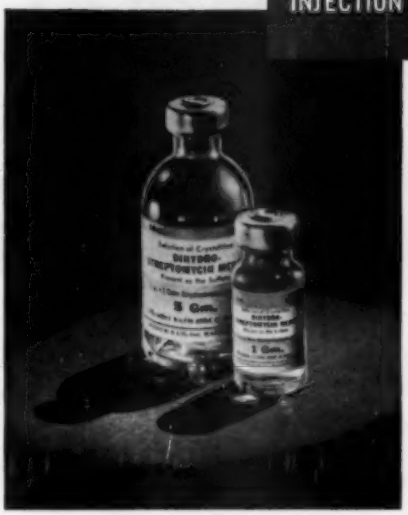

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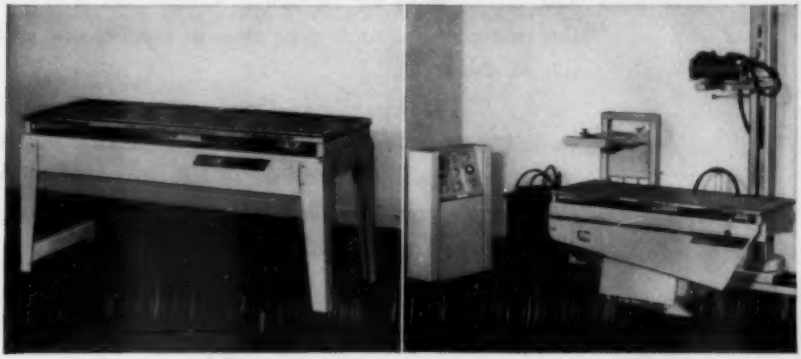

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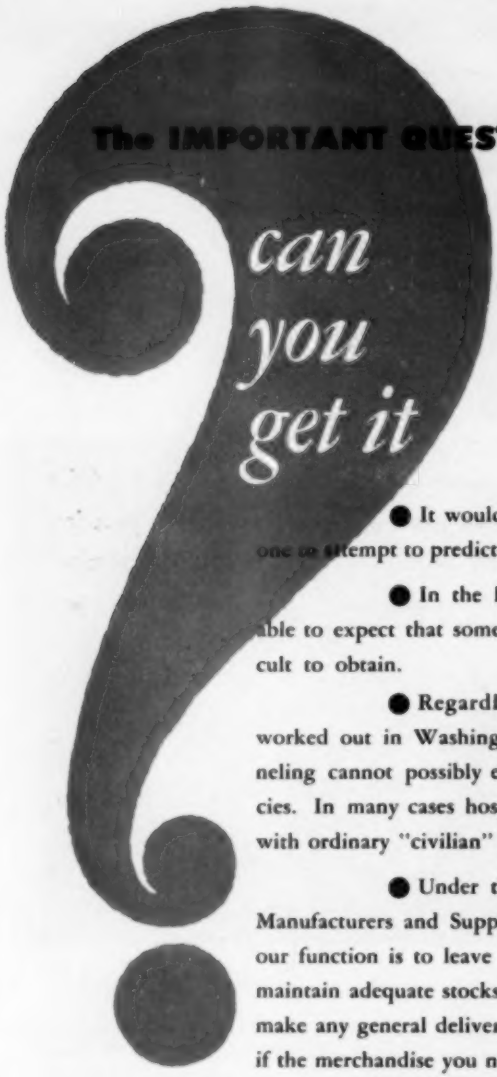

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ERRATUM

In Volume 63, No. 3, 1951, "Neurotoxicity of Dihydrostreptomycin", the last line of the first paragraph on page 314 should read "The latter investigators also reported the occurrence of hearing loss in 2 patients who received only 1.0 gm. of *dihydrostreptomycin* daily" instead of "The latter investigators also reported the occurrence of hearing loss in 2 patients who received only 1.0 gm. of *streptomycin* daily."

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TUBERCULIN-NEGATIVE TUBERCULOSIS[1]

WILLI MASCHER

(Received for publication December 26, 1950)

INTRODUCTION

On studying the abundant literature of recent years on tuberculin and the tuberculin reaction, it is evident that our knowledge of the subject is still very limited. Moreover, as Rich (30) has pointed out in an entire chapter devoted to "The Confusion in Terminology," fruitless ambiguities could be prevented if in discussing this subject the poorly defined and misused expression *allergy* (with all its derivatives: positive and negative anergy, et cetera) could be avoided. As he states, "It (the term allergy) has become a fertile source of confusion and misunderstanding." He illustrates where this misuse can lead by quoting a modern work in which it is stated: "This form of anergy represents the highest degree of hyperergy!"

There are, in fact, only two basic observations on the question of the significance of the tuberculin reaction on which there seems to be unanimity of opinion. One is the observation that persons not infected with tuberculosis are absolutely insensitive to tuberculin, even when administered in enormous doses. Moreover, persons not infected with tuberculosis cannot be rendered sensitive to tuberculin. Attempts to produce a typical tuberculin reaction in such persons with tuberculin or its different derivatives have never succeeded. In regard to allergic reactions, and anaphylactic and Arthus type of hypersensitivity, which are often confused with the tuberculin reaction, the reader is referred to the detailed discussion by Rich (30).

The other basic observation, the correctness of which is generally conceded, is that when the tuberculin reaction is positive it signifies that the subject tested harbors a tuberculous focus brought about by infection with living or dead *M. tuberculosis*. This interpretation of the reaction implies nothing about the activity or clinical significance of the existing focus. The strength of the reaction can vary, depending on different, to a large extent yet unknown, causes. Nevertheless, a weakly positive reaction does not by any means contradict the existence of an active tuberculous process, just as a strong reaction does not prove that such an active process is present.

By "tuberculin reaction" in the following article, only that local skin reaction

[1] From Södermanland District Sanatorium in Löt, Malmby, Sweden.

is referred to which can develop as the result of a correctly performed, intracutaneous injection of different dilutions of tuberculin. The reaction is said to be positive when there is an *infiltrated area* measuring at least 5 by 5 mm. with Pirquet's reaction, and at least 10 by 10 mm. with Mantoux technique (erythema alone at the site of injection is insufficient), which persists for at least forty-eight hours, preferably even for seventy-two hours. For practical purposes, a negative tuberculin reaction can be designated when there is a failure to react to intradermal injection of 1 mg. (dilution 1:100); some investigators, however, demand 3 or even 10 mg. A negative reaction to Pirquet alone, or a negative reaction to tuberculin ointment alone, cannot be considered as a negative tuberculin reaction.

In addition to the local skin reaction it is possible, by means of subcutaneous or intravenous injection of tuberculin, to produce a constitutional reaction. This manifests itself by focal reactions and in certain systemic reactions which can increase even up to a "tuberculin shock" with a fatal outcome. In man (and the following account applies to the tuberculin reaction in man) it is manifestly impossible to study the systemic reaction to tuberculin because of the risks involved. Moreover, despite all the work which has been devoted to the question, the composition and active components of tuberculin itself have not yet been completely explored. Pinner (29) says, for example, in 1947: "It is obviously a most complex and confusing mixture of substances."

Nevertheless, the tuberculin reaction would be a completely satisfactory procedure if it could be maintained that an undoubtedly negative tuberculin reaction proved that the subject tested was not infected with tuberculosis. This, however, is far from being the case. On the contrary, the researches of the past decade have shown that the previously recognized and easily diagnosed exceptions to this "rule" must, in several respects, be amplified, so that one must now recognize that it is not at all unusual for the tuberculin reaction to be negative even in individuals proved to be infected with tuberculosis. This fact is of such significance that it is well worth the trouble to recapitulate when such has been the case.

By means of *desensitization*, i.e., the application of increasing doses of tuberculin, it is possible to change a person's reaction to tuberculin so that it decreases in strength and eventually can no longer be elicited. According to many writers, the tuberculin reaction is the expression of a hypersensitivity produced by tuberculous infection which in the allergic body should coexist with (and, according to many investigators, be dissociable from) immunity. It has also been attempted for therapeutic purposes to remove this hypothetically dangerous "oversensitivity" by desensitization of tuberculous patients. Animal experiments have not given indisputable results, however, and the tuberculin treatment in man with desensitization in view has not enjoyed tangible success, and has been abandoned. An attempt has also been made to explain the negative tuberculin reaction after desensitization in the same way as in anaphylaxis, i.e., through an increase of antibodies to tuberculin. Efforts have even been made to demonstrate this antibody but with contradictory results. Nevertheless, the matter cannot be considered as settled. Rich (30) who, with his associates, has submitted these problems to very thorough

investigation, concludes his account by saying: "It would be unwise to accept at present any of the dogmatic pros and cons of the question."

The tuberculin reaction remains negative after infection has taken place for a certain *period of incubation*, a fact which is generally known but, nonetheless, occasionally gives rise to misdiagnoses. The incubation period can vary within considerable limits (twenty-three to sixty days or more). Moreover, one occasionally finds children with completely developed primary complexes, as seen on the roentgenogram who are still tuberculin negative. Not until after some time does the tuberculin reaction become positive. The diagnostic significance of this phenomenon is obvious.

The tuberculin reaction can also remain negative despite definitely proved *infection which "does not take."* With BCG vaccination, for example, the patient has been "infected" with *M. tuberculosis*. It is well known, however, that the tuberculin reaction may remain negative despite repeated BCG vaccination even with increased dosage. It is probable that a similar phenomenon occurs in an environment with natural possibilities of infection, as has been pointed out by several writers. Brailey (3) in 1940 found that 25 per cent of 306 children who had been living six to twelve months in tuberculous homes had remained tuberculin negative.

The present writer has observed a patient with fibrocavernous tuberculosis which, according to the history and appearance, was presumably several years old at the time of discovery. Four years previously the patient had had her first hemoptysis, which failed to cause her to seek medical examination. She had two children, one six and the other four years old. She had breast fed the children and had managed their entire care without help in a dwelling of one room and a kitchen. The 6-year-old child was a tuberculin reactor and had had a pleurisy. In contrast, the 4-year-old child consistently failed to react to tuberculin (up to 1 mg.) during the period of over one year after the mother was admitted to the sanatorium. It is hardly conceivable that this child could have avoided infection during the years with the mother who undoubtedly had been suffering the entire time from an "open" tuberculosis.

It is well known that the tuberculin reaction becomes negative *in cachetic individuals* not only where the cachexia is due to tuberculosis but also in other illnesses; for example, the cachexia of cancer.

The development of *certain nontuberculous infections* may be accompanied by a transitory diminution or abolition of the cutaneous sensitivity to tuberculin. In this connection it is usual to mention measles, and even pneumonia, whooping-cough, and others. It has been reported that in early syphilis the tuberculin reaction seems to diminish or disappear concurrently with the developing Wassermann reaction (Hellerström (9)). According to this writer, with the initiation of antisyphilitic therapy the tuberculin reaction becomes positive again, but in untreated cases may remain negative for months.

Lemming (18) and others point out that exposure to sunlight (ultraviolet treatment) may make the sensitivity to tuberculin decrease, and Pickrell (26) has reported that the same phenomenon occurs during intoxication with alcohol.

It should be noted that, according to many writers, in cases in this category the question must be a diminution of the reactive power of the skin brought about by toxic or other causes (in cachexia, according to Pilcher (27), by dehydration) and thus not by any form of desensitization. A positive tuberculin reaction is conditioned by the physiologic state of the skin. If this is altered from the normal, the skin may lose its ability to react to a number of stimuli, not only tuberculin but other nonspecific irritating agents as well. Pilcher (27) showed, in 1930, that in progressive tuberculosis the sensitivity to tuberculin diminishes concurrently with the fall in the patient's weight. The same occurs with such

complications as miliary spread of tuberculosis, measles, and other conditions. In these cases, however, the reactive power of the skin diminishes also towards nonspecific irritants, for example, codein. Parodi (24) believes that the tuberculin reaction is a function of the condition of the skin and should be studied rather by means of chemical and physical methods than by means of methods of classical immunology. In a large-scale investigation in 1947 of the conditions of resorption in the skin, Seeberg (31) has shown that a definite relation exists between the result of intradermal reactions and the "disappearance time" of a standard wheal, for example, one produced by sodium chloride. He noted that the quicker the absorption of the standard wheal, the weaker the reaction to other stimuli. This holds true both for allergic and for toxic skin reactions.

The tuberculin reaction is often negative in hematogenous spread such as *miliary tuberculosis and meningitis*. According to Rich and others, these cases represent a true desensitization. These investigators are of the opinion that the sensitivity to tuberculin is extinguished when strongly toxic tuberculous material (bacteria or caseous necrotic material) is suddenly discharged into the blood stream or into body compartments from which rapid absorption can occur. In such situations, a condition should arise similar to that seen when a large, but not lethal, dose of an antigen is introduced into an anaphylactic host, namely, an "exhaustion or neutralization of antibody." Rich (30) describes two cases where a caseous focus had perforated into the pleural cavity and caused an acute pleurisy. Both patients became negative reactors to 1 mg. of tuberculin; later they again reacted positively to 0.01 mg. Pilcher (27) describes a patient who previously during his sanatorium stay had reacted to 0.01 mg. of tuberculin, but became negative up to 10 mg. when he developed a miliary tuberculosis. To a nonspecific agent (codein), the patient's cutaneous reaction was normal, however, which showed that the question was not one of the skin's inability to react but of a true desensitization.

The tuberculin reaction may also *spontaneously change to negative in clinically healthy tuberculin-positive individuals*. It has long been the prevailing opinion that an individual who has once been positive should retain this mode of reacting throughout life. In the later years, however (first in America, then in other countries also), numerous works have been published which show that this is not the case at all. If a careful investigation is conducted of a group of tuberculin-positive healthy individuals in such a way that the tuberculin tests are repeated at appropriate intervals during several consecutive years, a certain number of persons will be found to have reverted to the negative reaction.

These investigations at first met with sharp criticism and mistrust; the possibility of technical errors in the performance and reading of the reaction together with pseudo reactions and other sources of error was pointed out, for example, by Jakobsson (13). Certain of these comments are undoubtedly justified. Expressions such as "weakly positive tuberculin reaction" ought to be abolished; they are worthless without information of the dosage and the measurements of the reaction in millimeters. The same investigator preferably should undertake all of the readings. Moreover, no definite conclusions can be drawn from comparisons between investigations carried out with, for example, Pirquet or tuberculin ointment in the first test and by the Mantoux technique in the subsequent tests. Such technical errors may well have been committed in not a few of the investigations cited. Nevertheless, a large number of careful studies have been published which show, without any doubt, that one must reckon with the possibility of a "reversion" from positive to a negative tuberculin reaction in such clinically healthy individuals.

The frequency of such a change is given very differently by different writers. Keller and Kampmeier (14) studied 139 medical students and nurses and found "reversion" in 21.5 per cent four years later (tested up to 1 mg.). Dahlstrom (4) found that, among 2,490 persons retested after five to fifteen years, 11.1 per cent had "reverted" (1 mg.).

The majority of investigators, however, arrive at considerably lower figures for the incidence of the disappearance of the state of cutaneous reactivity to tuberculin. Lloyd and MacPherson (21), for example, found on retesting 200 children after two years that 2 per cent had "reverted," as judged by failure to react to 1 mg. of tuberculin. Zacks and Sartwell (39) in 1942 found a "reversion" incidence of 3 per cent among more than one thousand retested after ten years (12.7 per cent among five- to fourteen-year-olds; 1 per cent among those more than twenty years of age who were examined). Törnell (35) in 1943 estimated the number of "reversions" in his material as 0.1 per cent annually, and Andenaes (1) found "reversion" after a lapse of six to seven years in 0.2 to 0.3 per cent.

In addition, it appears clearly from these investigations that the frequency of "reversion" is much greater in those cases which have previously reacted weakly, or only to the larger tuberculin doses, than in those cases in which an initial strong reaction to small doses was observed. In a table published by Törnell (34) concerning the result of the reaction in such repeated investigations, isolated cases are recorded in which the reaction was alternately positive and negative. Recently (1950), Tukey, Dufour, and Seibert (36) have observed the same phenomenon (alternating positive and negative reactions) in testing student nurses every three months during their period of training.

Pinner (29) states rightly that we do not know what morphologic, bacteriologic, or immunologic changes cause a positive reaction to become permanent in a clinically healthy individual. It might be supposed that the reaction was extinguished when living bacilli were no longer found in the host. This has never been proved, however, and indeed seems improbable. Many persons with primary complexes which are sterile as far as they can be judged, and without other demonstrable foci, remain positive throughout life. On the other hand, it seems as if individuals in an environment free from tuberculosis more often "revert" than those who are exposed to repeated infections. This phenomenon might tend to provide support for the theory that repeated super- or re-infections are necessary for the persistence of the tuberculin reaction. In any case, the writer is in agreement with Pinner that an unknown and probably growing percentage of persons without demonstrably active tuberculous changes, but who react positively to tuberculin, "revert" to negative reactions in the course of the years. The precise explanation of the phenomenon is not known.

It has been shown, both in animal experiments and in man, that the tuberculin reaction can become negative concurrently with the occurrence of *biologic healing*.

Anatomic healing can only be recognized in those cases in which the persons concerned react to a new infection as if they had not been previously infected, e.g., with a new typical primary lesion alongside the yet demonstrable calcified primary complex. Such cases are described with both roentgenographic and pathologic observations. It must be mentioned, however, that calcification in the lungs or other organs is not always necessarily a relic of a tuberculous infection. In several works, particularly American, it is pointed out that encrustation with calcium may occur even in other illnesses (histoplasmosis, for example). Nevertheless, Olsen-Böje (23) in 1949 found, among 396 cases with demonstrable calcification, only one in which the tuberculin reaction was negative; moreover, histoplasmosis has hitherto not been demonstrated in Scandinavia.

A typical primary complex occasionally may even be seen to develop after the "resistance" has disappeared following BCG vaccination. Such a case, verified on pathologic-anatomic grounds, has been observed by Hedvall (personal communication).

According to Rich (30), negative tuberculin reactions up to 10 mg. can be found in cases of healed tuberculosis, despite the fact that virulent bacilli are still present in the healed lesions. He postulates that the bacilli still viable in such cases are no longer able to excrete specific antigens.

. . . and there is evidence, that the bacilli in the arrested lesion may cease to proliferate, but nevertheless remain alive for a considerable period of time in a state of inactivity. In such a state there is no reason to believe, that any appreciable amount of sensitizing antigen would be liberated from the bacilli.

The loss of sensitivity to tuberculin should in such cases depend on a continual diminishing of sensitizing "antibodies." This is not proved, however, for the demonstration of any sensitizing antibody in conjunction with the tuberculin reaction has not yet been made, despite the numerous reasons which speak for its existence. Pinner (29) also points out that we do not know whether the negative tuberculin reaction in healed tuberculosis has anything to do with the anatomic healing of the focus or with the disappearance of bacilli from the focus. "It seems entirely safe to conclude that the presence of viable tubercle bacilli is not a necessary condition for the persistence of tuberculin allergy."

In *old age* negative tuberculin reactions are often found. In some cases this can probably be explained by the fact that the tuberculous lesions are biologically healed; in other cases the lack of reaction depends perhaps on a failing general reactivity of the skin. In the majority of cases, however, the cause of the negative reaction cannct be demonstrated.

Among 862 old people, Lemming (18) found that 6 per cent were tuberculin negative to 1 mg. (3 of these reacted, however, to 3 mg.); in addition, he refers to further cases observed by him, making a total of 65 tuberculin-negative old people. Of these, 18 had roentgenographic signs interpreted as evidence of previous tuberculosis. In 5 cases examined post mortem, on the other hand, no demonstrable sign of tuberculosis was found. Malmros (cited by Lemming (18)), in a group of 142 old people, found that 2 per cent were tuberculin negative, but his material was taken from a mental hospital where cases of "open" tuberculosis were also found. Holm (10) found that 11 per cent of 224 old people were negative to 1 mg. of tuberculin.

The type of cases described above, in which a negative tuberculin reaction occurred in a person previously infected with *M. tuberculosis*, should give rise to no difficulties in differential diagnoses. Moreover, cases of this sort can be regarded as being more of epidemiologic than clinical interest as far as clinically healthy individuals are concerned. There is a group of cases, however, which is of much greater clinical significance, namely, the patients with *active tuberculosis and negative tuberculin reactions* in whom none of the causes mentioned above can be recorded as a reason for this mode of reaction. These patients are in good general condition and are not suffering from intercurrent illnesses or the like.

Such cases have been regarded as uncommon and the few relevant publications as a rule describe only isolated cases as being rarities. In 1943, however, Hevall (7) reported a series of 7 cases. In all of these reports the cases were thoroughly investigated and there can be no doubt that the patients suffered from active tuberculosis, yet failed to react even to large doses of tuberculin.

Only scanty information of the frequency of such cases is available and apparently all of the cases reported were found in sanatorium material. In 1932, Hart (cited in (10)) found that 2.7 per cent of a series of 463 cases with pulmonary tuberculosis failed to react to 1 mg. of tuberculin and 3 per cent did not react to 3 mg. (a surprisingly high number). Kvinnsland (17) found 2 cases negative to 1 mg. of tuberculin despite good general condition among 4,000

tuberculous patients admitted to Ringvål Sanatorium. Lichtenstein (20) give an account of 11,749 patients admitted during the years 1932 to 1946, of whom (excluding the cachectic and senile) 142 were tuberculin negative. Of these, 138 were found to be nontuberculous, but 4 (3 per cent) of the tuberculin negative or 0.03 per cent of the total had active tuberculosis.

The significance of such clinical material chosen from among sanatorium patients may be criticized on the ground that the patients represent a selected group. It is probable that a considerable number of those admitted to the tuberculosis hospitals had been previously tested with tuberculin. As a consequence, the negative cases would have been sifted out and regarded as nontuberculous in spite of the fact that a closer examination might have shown that in a number of the patients tuberculosis was present despite the negative tuberculin reaction.

The present writer studied the tuberculin reaction in 5,623 persons in whom miniature roentgenograms were considered to show pathologic changes. The study was made in the course of a mass miniature roentgenographic examination of the population of the administrative district of Södermanland, which included 97 per cent of the 178,344 inhabitants of the district more than seven years of age. Of these 5,623 persons, 196, or 3.5 per cent, were found to be negative to tuberculin in doses as high as 1 mg. On further investigation, it was found that 188 of the 196 persons were either completely healthy or were suffering from some affection other than tuberculosis. Among the 1,591 persons who after control examination were registered as suffering from tuberculosis, 8 still remained who were tuberculin negative. These 8 persons represented 0.14 per cent of all those examined (those suspect after miniature radiography) or 0.5 per cent of those with active tuberculosis. The findings might thus be expressed: *that of 196 tuberculin-negative persons with suspicious findings in the mass miniature roentgenograms, 4.07 per cent were found to be suffering from active tuberculosis.*

Thus, summarizing the conditions in which a negative tuberculin reaction can be found, despite the fact that a tuberculous infection undoubtedly must have occurred, the following possibilities are found:

1) After desensitization
2) During the incubation period
3) When the infection "has not taken" (for example after BCG vaccination or natural infection)
4) In cachexia
5) In miliary spread of tuberculosis
6) (Transitory) during the course of certain nontuberculous infectious diseases
7) In "reversion" of previously tuberculin-positive, clinically healthy individuals
8) In biologically healed tuberculosis
9) In old age
10) In certain cases of active tuberculosis in which none of the above mentioned conditions can be demonstrated.

The frequency of occurrence of the phenomenon, particularly under the categories 7 to 9, is difficult to estimate, but is probably becoming larger as super-

infections and reinfections should probably continue to decrease with the diminishing frequency of tuberculosis. In such circumstances it is clear that the epidemiologic conclusions which are usually drawn from the result of mass tuberculin testings may become more and more unreliable. *The number of tuberculin reactors is no longer an absolute index of the number of persons infected with tuberculosis* in a population subjected to examination, for an increasing number of infected persons may be found even in the tuberculin-negative groups. For practical clinical purposes it is particularly important to remember that a *negative tuberculin reaction in a case of suspected pulmonary disease does not exclude tuberculosis*, even in a patient who is in good general condition and is free from intercurrent nontuberculous infection. Therefore, suspicion of the presence of tuberculosis based on clinical or roentgenographic grounds must not be rejected because the tuberculin reaction proves to be negative. It is also evident that the exclusion of all tuberculin-negative individuals from examination by miniature roentgenography when mass examinations are carried out may result in a number (probably very small) of cases with tuberculosis remaining undiscovered. This risk must be considered larger, however, when environmental examinations for the tracing of the source of infection of newly discovered fresh infections are concerned. Hence, *in environmental examinations the persons who react negatively to tuberculin (at all events, the adults) should be examined roentgenographically*, for it cannot be assumed with absolute certainty that such individuals are free from tuberculosis.

OBSERVATIONS

In the sanatorium in Lőt, 11 cases of active tuberculosis with negative cutaneous tuberculin reactions have been observed in patients who were in good general condition and free from intercurrent nontuberculous infections. Of these, 8 were discovered by the above mentioned mass miniature radiography in the administrative district; the remaining 3 were discovered during the past four years' routine work at the hospital.

MATERIALS AND METHODS

The tuberculin test has always been carried out by intracutaneous injection of tuberculin according to the Mantoux technique. In the majority of cases, the Mantoux tests have been performed and interpreted by the writer or one of his associates. In some outpatients, the Mantoux test has been made, and the results interpreted by the doctors or the nurses of the local tuberculosis dispensary. These nurses have undergone special training for work of this kind. In the following discussion, the term *positive reaction* means that an area of induration developed which measured at least 10 by 10 mm. and persisted for seventy-two hours. A *negative reaction* means that no reaction whatsoever was visible after the intracutaneous injection of at least 1 mg. of tuberculin. In those cases in which *erythema* (without any trace of induration) persisted for seventy-two hours, this fact is especially indicated; in all other cases, the area of involvement measured represents induration. The tuberculin used consisted of solutions of Old Tuberculin freshly prepared in the state bacteriologic laboratory. Throughout the entire period, the same tuberculin solutions were used in routine work in the sanatorium and in the central dispensary, thus providing a good control of the reliability of the solutions.

In 7 cases, as much as 3 mg. of tuberculin were used; in the other 4 cases, the largest injection was 1 mg. All of the patients were tested repeatedly.

Tubercle bacilli have been sought by direct examination of smears of sputum as well as by cultures (Löwenstein-Hohn) and guinea pig inoculations with sputum and gastric washings. In several cases the colonies growing on the Löwenstein cultures have been inoculated in guinea pigs in order to avoid any confusion with acid-fast saprophytes.

The BCG vaccine used is prepared at the Bacteriological Laboratory in Gothenburg. This vaccine is approved by the WHO and by the International Tuberculosis Campaign of the UNICEF.

A short description of the cases follows:

1. Patients from Whom M. Tuberculosis Was Cultured (6 Cases)

Case 1. The patient (K. A. G.) was a male office worker who was born in 1908. His mother died from "inflammation of the lungs" in 1914; one sister died in childhood from "brain fever" in 1913. The other 8 siblings were all tuberculin positive, but were without roentgenographic evidence of tuberculosis. The patient had had "inflammation of the lungs" in 1930. He had never been examined roentgenographically or been tested with tuberculin. He had considered himself to be healthy and had been employed at full-time work until October 1947 when a chest roentgenogram revealed a shrinking fibrocavernous process in the right upper field. In the left middle field there was fresh spreading of partly confluent soft-spotted foci with suspected central softening. On admission to this hospital he had low-grade fever, but he soon became afebrile. He was treated with bilateral artificial pneumothorax with apparent success.

Bacteriologic examinations: Acid-fast bacilli were seen in the sputum and *M. tuberculosis* was cultured on Löwenstein medium. The culture was virulent on guinea pig inoculation. Sputum culture was still positive one year later, and the culture was again demonstrably virulent on guinea pig inoculation. Thereafter direct sputum examinations were negative.

Tuberculin reactions: In March 1948, the tuberculin tests were as follows: 0.01 mg., negative; 0.1 mg., 5 by 5 mm. erythema; 1 mg., 5 by 5 mm. erythema (without induration). On April 1 and 24, 1948, the reaction to 1 mg. was negative. On June 14, 1948, after injection of 1 mg., a 5 by 8 mm. erythema without induration was noted. The reaction to 1 mg. was also negative on July 20 and on September 2, 1948, and on May 10, 1949, and was negative to 3 mg. on May 15, 1949.

BCG vaccination: A diagnostic BCG test, according to Ustvedt's method, was performed on May 18, 1949 and resulted in neither early nor delayed local reaction. Mantoux tests to 1 mg. and 3 mg. were negative on July 28, 1949, and were negative to 1 mg. on February 2, 1950.

The patient was discharged from the sanatorium in very good general condition, and the bilateral pneumothorax has been maintained on an ambulatory basis.

Case 2. The patient (P. G. B.) was a motor mechanic who was born in 1913. His father died from tuberculosis in 1924. A miniature roentgenogram in 1944 shows "spots" on the lung, but the patient was tuberculin negative and, therefore, no further steps were taken. A second miniature roentgenogram in October 1946 revealed somewhat sparse fibroses in the right upper field and in the left apical area. In both hilar regions there were plum-sized lymphatic enlargements with polycyclic outlines. The patient was subjectively healthy, working full time, and he refused sanatorium treatment.

Tuberculin reactions: Mantoux tests with 0.01 and 0.1 mg. were negative. With 1 mg. there was a 5 by 5 mm. induration; but with 3 mg. there was a 10 by 10 mm. erythema without induration.

During the continued observation in the central dispensary steady increase was noted in the roentgenographic shadows in both upper fields. The erythrocyte sedimentation rate and general condition were normal throughout. In October 1947 acid-fast bacilli were demonstrated in direct sputum examination, and the patient was admitted for treatment.

The patient was a powerfully built man in good condition. He was afebrile and the eryth-

rocyte sedimentation rate was 3 mm. in one hour. Roentgenographic examination revealed a thin "fibrosis" and shadows like thin, partly confluent specks in both upper fields. The enlarged lymph nodes in the hilar areas were unchanged.

Bacteriologic examination: Culture and guinea pig inoculation from stomach washings obtained in October 1947 were positive for *M. tuberculosis*. In December 1948 gastric washings were negative on culture and guinea pig inoculation.

Tuberculin reactions: During the period October to December 1947, Mantoux tests with 1 mg. of OT were negative. In January 1948 a Mantoux test with 3 mg. was performed; after seventy-two hours there was an erythema of 8 by 10 mm. but no induration. The reaction was negative the following day.

BCG vaccination: The patient refused BCG vaccination.

Examination was carried out with Besnier-Boeck-Schaumann's disease (sarcoidosis) in mind, but nothing positive was found which could support the diagnosis. Unfortunately the patient moved his place of residence and his further progress could not be followed.

Case 3. The patient (A. A. W.) was a housewife who was born in 1896. There was no family history of tuberculosis. The patient's husband and 3 grown children were tuberculin positive, but all had chest roentgenograms which were negative for tuberculosis. One grown daughter had been tuberculin negative and became a positive reactor after BCG vaccination. In 1927 the patient had been treated for "slime in the lungs." In 1928 and the following years she had had "asthma" but during recent years she had only rarely been troubled by it. She had never been tested with tuberculin. Miniature and conventional roentgenography in 1947 revealed pleural thickening over both apical areas. In the left apex fibrosis with calcification was found, and in the right apex there was fibrosis with moderate contraction and spot-shaped, nonconfluent, ill-defined foci of more recent appearance. The patient was in good general condition, was afebrile, and the erythrocyte sedimentation rate was persistently between 20 to 30 mm. in one hour.

Bacteriologic examination: In October and November 1947, acid-fast bacilli were found in the sputum and the specimen of November 11 was positive for *M. tuberculosis on culture*. Guinea pig inoculation from the culture was unfortunately unsuccessful because both guinea pigs died from intercurrent disease. Two subsequent guinea pig inoculations with sputum and one culture of sputum were negative for *M. tuberculosis*, and acid-fast bacilli could no longer be demonstrated in a majority of direct sputum examinations.

Tuberculin reactions: In November 1947 intracutaneous injections of 0.01 mg., 0.1 mg., and 1 mg. of OT, respectively, all failed to evoke a reaction. The results were similarly negative with 1 and 3 mg. in February 1948 and with 1 mg. in September 1949 and June 1950.

BCG vaccination: The patient was vaccinated with BCG in July 1950. By September 1950 no local reaction had appeared and there was no reaction to the intracutaneous injection of 1 mg. of OT.

Unfortunately this patient refused bronchoscopy, an examination which would have been of great interest in investigating possible tuberculosis of the mucous membrane.

Case 4. The patient (G. V. E.) was a building laborer who was born in 1911. There was no family history of tuberculosis. The patient's wife and a 12-year-old daughter were both tuberculin negative and without roentgenographic evidence of tuberculosis. The patient had had "catarrh of the lungs" in childhood, "inflammation of the lungs" in 1926, and "wet pleurisy" in 1942. During the last-named illness he was cared for at home for six weeks, but no roentgenograms or tuberculin tests were obtained. Miniature and conventional roentgenograms in 1947 revealed that the right diaphragmatic arch was flattened, the sinus was obliterated, and there was extensive pleural thickening laterally. In the apical area and in the first interspace, cloudy nonconfluent parenchymatous foci were present. In the middle area, there was a veil-like condensation in which some obloid thinnings not unlike bronchiectasis were discernible. Also at the left base behind the heart the pattern of the shadows resembled those of bronchiectasis. The patient was afebrile, with an erythrocyte sedimentation rate of 30 mm. in one hour, and he was in good general condition.

Bacteriologic examination: In November 1947 acid-fast bacilli, presumably tubercle bacilli, were found in the sputum. Culture and guinea pig inoculations from the sputum were positive for *M. tuberculosis*. In February and in November 1948, the sputum was negative for *M. tuberculosis* on both culture and guinea pig inoculation.

Tuberculin reactions: In November 1947 the Mantoux test was negative to both 1 mg. and 3 mg. OT. In February 1948, the reaction was again negative to 1 mg. OT.

BCG vaccination: On February 25, 1948 the patient was vaccinated with BCG. The procedure was not followed by either an early or a late local reaction. On April 23, 1948 the Mantoux test to 0.05 mg. was negative, but there was a small induration (3 by 4 mm.) after the injection of 1 mg. In February 1949, the Mantoux tests to 0.1 mg. and 1 mg. were both negative.

The patient moved his residence and was lost from observation.

Case 5. The patient (E. W.) was a farm worker who was born in 1914. His father and two siblings died from tuberculosis. The patient's wife and two children, 11 and 13 years of age, were all tuberculin positive, but without roentgenographic evidence of tuberculosis. The patient had come as a refugee to Sweden in 1944 and had had no previous roentgenographic examinations there, apparently because he had moved about a great deal. For one year he had been tired and had coughed and expectorated, but was able to work full time. The diagnosis of tuberculosis was made in 1949 when he applied for a medical certificate for emigration. The patient was a powerfully built man who was somewhat thin, but otherwise in good general condition. He had a low-grade fever for approximately one month, but was subsequently afebrile. The erythrocyte sedimentation rate was 40 mm. in one hour and later fell to 20 mm.

Roentgenographic examination revealed tuberculous changes down to the fourth rib in both lungs; on the right side the changes were confluent with a cavity laterally in the second interspace; on the left side the shadows were thinner with a more fibrous appearance. The patient has shown considerable improvement on treatment with artificial pneumothorax.

Bacteriologic examination: On admission in September 1949, *M. tuberculosis* was found in the sputum by direct examination, culture, and guinea pig inoculation. In December 1949 culture of the sputum was still positive for *M. tuberculosis*, but since that time tubercle bacilli have not been demonstrable.

Tuberculin reactions: On September 22, 1949 the Mantoux test with 1 mg. of OT was negative, and on October 13 and November 16, 1949, tests with 3 mg. were negative.

BCG vaccination: In November 1949 a diagnostic BCG test by Ustvedt's method was performed, but there was neither an early nor a late reaction. On January 9, 1950 the Mantoux test to 0.1 mg. was negative. With 1 mg. no reaction was seen at twenty-four hours; after forty-eight hours there was an erythema of 10 by 15 mm. and at seventy-two hours there was a weak, hardly visible erythema, measuring 20 by 20 mm., which disappeared during the ensuing twenty-four hours.

Vaccination with human-virulent M. tuberculosis: In May 1950 the patient was vaccinated with tubercle bacilli obtained by culture of his sputum. Three weeks later papular tuberculides developed at the site of vaccination.

On September 6, 1950 the Mantoux test with 1 mg. was positive with an induration of 10 by 12 mm., and on September 9, 1950 the reaction was positive to 1 mg. with an induration of 10 by 10 mm. Two months later, however, on November 5, 1950, the reaction to 0.01 and 0.1 mg. was negative, and with 1 mg. there was only erythema of 8 by 10 mm. without induration.

Case 6. The patient (G. G. L.) was a building laborer who was born in 1891. A cousin died from tuberculosis in 1935; otherwise there was no familial history of the disease. The patient's wife was tuberculin positive but roentgenographically negative for tuberculosis. A 10-year-old stepdaughter was tuberculin negative and became tuberculin positive after

BCG vaccination. Miniature roentgenography in 1947 showed calcification in the right hilar region with no other definite abnormalities.

Roentgenographic examination in May 1950 revealed a large, cup-shaped calcium formation at the right hilus. Under the clavicle, stretching towards the base, were striated and spotted changes and coarse-spotted, almost ball-shaped, foci which first raised the suspicion of tumor metastases. On the left side increased striation was noted but no definite formation of a focus. The patient's general condition was good, with only a low-grade fever and an erythrocyte sedimentation rate ranging between 20 and 30 mm. in one hour.

Bacteriologic examination: M. tuberculosis was found on microscopic examination and guinea pig inoculation of the sputum.

Tuberculin reactions: The Mantoux test in February 1950 (by a private doctor) was negative to 1.0 mg. In May 1950 (in hospital) the reaction was negative to both 1 and 3 mg. On admission to the sanatorium on July 10, 1950, the Mantoux test with 0.01 mg. and 0.1 mg. was negative; with 1 mg. there was distinct induration measuring 10 by 12 mm. with an erythematous area 25 by 30 mm. In August 1950 the Mantoux test was again negative to 0.01, 0.1, 1, and 3 mg., and in September 1950 tests with 1 mg. and 3 mg. were also negative.

Investigations with Besnier-Boeck-Schaumann's disease (sarcoidosis) in view, including pathologic-anatomic examination of a removed tonsil, revealed no abnormalities.

II. Patients from Whom M. Tuberculosis Was Not Cultured But Who Had Acid-fast Bacilli (Presumably M. Tuberculosis) in Sputum (2 Cases)

Case 7. B. B. was a farmer who was born in 1920. There was no family history of tuberculosis. His 64-year-old mother was tuberculin negative, his two children were tuberculin positive, and two siblings were tuberculin positive. All of these relatives had chest roentgenograms negative for tuberculosis. The patient had had erythema nodosum in 1936, at which time roentgenographic examination in another institution had revealed no abnormalities. His tuberculin reaction was not tested at that time and his case was not followed. He had had "asthma" since 1937 and had been troubled with bronchial symptoms in the first years, but improved recently and was working as a full-time farmer.

In October 1948 miniature and standard-sized roentgenograms revealed pleural thickening over the left apical area with sparse "fibrosis" beneath. Over the right upper field there were distinct foci in spotlike and sweeping forms, probably containing calcium. There was definite calcium at the right hilus. In addition, bilateral moderate emphysema was present. The patient was in good condition although somewhat thin. He was afebrile and the erythrocyte sedimentation rate remained between 15 and 28 mm. per hour.

Bacteriologic examination: In November 1948 and in February 1949 acid-fast bacilli morphologically characteristic of *M. tuberculosis* were found in direct sputum examinations; thereafter a majority of such examinations were negative. The patient refused to cooperate and, hence, sputum cultures were not obtained.

Tuberculin reactions: In November 1948 the cutaneous reaction to 0.05 mg. of OT was negative, as was the reaction to 1 mg. The Mantoux test in February 1949 was negative to 1 mg. and was also negative in July 1949.

BCG vaccination: In August 1949, BCG vaccination was performed and there was no early reaction. In October 1949 a little papule developed at the site of vaccination. At this time the Mantoux test to 0.05 mg. was negative. When 1 mg. of OT was injected, a definite induration barely 10 by 10 mm. appeared and persisted for one week.

Unfortunately, the patient refused stomach aspiration and also bronchoscopy procedures which were proposed on account of the suspicion of tuberculosis of the bronchial mucous membrane.

Case 8. The patient (K. Å. J.) was a cattle steward who was born in 1911. His mother had been treated several times for tuberculosis since 1914, but she died in 1920 from another illness. The patient's wife and two children (17 and 18 years of age) were tuberculin positive

without roentgenographic evidence of tuberculosis. A chest film of the patient (a defective print) taken in 1936 revealed a suspicious spottiness in the left supraclavicular region and first intercostal space, for which no treatment was instituted. He was not tested with tuberculin at that time. Miniature and conventional roentgenograms in August 1948 revealed distinct specks in the first right interspace, and on the left side down to the third rib there were coarsely spotted, partly cloudy foci with a suspicious thinning laterally in the first interspace. Tomographic examination revealed a cavity the size of a peanut in the first interspace. The patient was in good condition, was afebrile, and had a normal erythrocyte sedimentation rate. Left-sided artificial pneumothorax was induced immediately after admission.

Bacteriologic examination: Acid-fast bacilli, presumably *M. tuberculosis*, were found in the sputum before the institution of collapse therapy, and on one occasion soon thereafter. Cultures and guinea pig inoculation of the stomach washings (performed three months after induction of artificial pneumothorax) were negative for *M. tuberculosis*.

Tuberculin reactions: On September 7, 1948 the Mantoux test with 0.01 mg. of OT was negative. Repeated testing was neglected from then onward, a fact which unfortunately was not discovered until December 1948. At that time there was no reaction to the intracutaneous injection of successive doses of 0.01, 0.1, 1, and 3 mg., respectively. In January 1949 the reaction to 1 mg. of OT was again negative. On February 2, 1949 the injection of 1 mg. of OT produced a 7 by 7 mm. erythema with indistinct induration. The reaction to 0.05 mg. was negative on February 28, 1950 but was positive to 1.0 mg. with a 15 by 15 mm. distinct induration. Since then the patient has remained unmistakably positive for 1 mg. but negative when tested with 0.01 and 0.1 mg. of OT.

Treatment with artificial pneumothorax continues; the patient is working and is in good condition.

III. Patients with Roentgenographic Abnormalities Considered to Be Tuberculous in Origin But in Whom Bacteriologic Proof of Tuberculosis Was Not Obtained (3 Cases)

Case 9. The patient (K. H.) was a widow who was born in 1894. Her husband died from tuberculosis in 1940, and two cousins died from tuberculosis in 1944. The patient's two grown children were Mantoux positive, without roentgenographic evidence of tuberculosis. Roentgenographic examination in 1948 revealed a calcified primary complex on the right side, with calcium in the left hilar region. In the right mid-lung field and the left apical area and first intercostal space there was fibrous and partly distinct spottiness. Moreover, on the left side there were several cloudy, coarse-spotted foci. The erythrocyte sedimentation rate was persistently raised to 30 to 40 mm. in one hour. The patient's general condition was good. She was afebrile, but thin and somewhat pale (anemia, chronic gastritic). There were no roentgenographic changes during the period of observation.

Bacteriologic examination: In February 1949, 3 direct sputum samples were negative for tubercle bacilli. In March 1950 culture and guinea pig inoculation of the stomach washings were negative for *M. tuberculosis*.

Tuberculin reactions: In November 1948 and in April 1949 the reaction to 1 mg. of OT was negative and was again negative in February and in May, 1950.

BCG vaccination: On June 5, 1950 the patient was vaccinated with BCG. After four days, an erythema of 4 by 5 mm. appeared at the site of vaccination, and six days later a blanched erythema 5 by 6 mm. was present without papule. Five weeks after vaccination there was a strong local reaction, with discharging papule which healed about a month later. In September 1950 the Mantoux test with 0.05 mg. OT was negative; with 1 mg. OT there was a 10 by 15 mm. erythema without a trace of induration; and with 1.5 mg. OT there was an erythema of 15 by 20 mm. with no induration.

Case 10. The patient (K. N.) was a schoolgirl who was born in 1936. Her mother had suffered from pulmonary tuberculosis since 1945 but tubercle bacilli had never been demonstrated in her sputum. In the examination of the family at that time (1945) the girl was tuberculin negative to 1 mg. of OT and, despite BCG vaccination, remained negative to 1 mg. (erythema 6 by 8 mm.). In the spring of 1948 the mother became ill with an acute spread and excavation of her disease and the sputum became positive for *M. tuberculosis*. At the same time the child developed "inflammation of the lungs," was admitted to the hospital and treated with sulfonamides and penicillin. Not until approximately four weeks later did she become afebrile, but the roentgenographic changes receded to only an insignificant extent. As the guinea pig inoculation of stomach washings was negative for tubercle bacilli, however, and as the tuberculin reaction was negative to 0.01 mg. and 0.1 mg., and "hardly positive" (8 by 10 mm.) to 1.0 mg., the diagnosis of tuberculosis was considered improbable. Nevertheless, the patient was placed under observation at the central dispensary. Roentgenographic examinations showed unmistakably enlarged lymph nodes at the left hilus and a focus the size of a plum, with indefinite borders at the left base. During the succeeding period the girl lost weight and had a persistent low-grade fever. As a certain progress of the process at the left base could not be excluded and the enlarged lymph nodes remained unchanged, she was admitted to the sanatorium where she remained from August 23 to October 25, 1948. Her general condition was good; she had a low-grade fever but became afebrile after a few weeks. The erythrocyte sedimentation rate was approximately 10 mm. in one hour. The roentgenographic changes persisted stubbornly and not until about a year later did a substantial regression occur. At present, after almost two years' observation, the enlarged lymph nodes have disappeared (no calcification is visible, however), and of the infiltrate at the base of the lung only an intensified striation remains.

Bacteriologic examination: M. tuberculosis could never be demonstrated in the sputum despite two further cultures and guinea pig inoculations.

Tuberculin reactions: The Mantoux test was negative on the following occasions: August 26, 1948 to 0.01 mg.; August 28, 1948 to 0.1 mg. (erythema 5 by 5 mm.); August 31, 1948 to 0.1 mg.; September 3, 1948 to 1 mg. (erythema 4 by 7 mm.); September 10, 1948 to 1 mg.; September 23, 1948 to 1 mg. (after twenty-four hours, erythema 7 by 10 mm.; after forty-eight hours, erythema 15 by 17 mm. without a trace of induration; after seventy-two hours, erythema 10 by 10 mm., disappearing in the next twenty-four hours); on October 21. 1948 to 1 mg. (erythema 10 by 10 mm. at forty-eight hours, gone at seventy-two hours). In two tests in the spring of 1949 the reaction to 1.0 mg. OT was still negative.

BCG vaccination: On September 25, 1949 the patient was vaccinated with BCG. At the site of inoculation an area of infiltration the size of a pea developed after approximately three weeks and remained for a long time, with slight discharge. In November 1949 the Mantoux test with 0.05 mg. OT was negative, but with 1 mg. the reaction was positive, with a distinct induration 12 by 12 mm. in diameter. The reaction has subsequently remained positive to the same dose of OT.

Despite the fact that *M. tuberculosis* was not demonstrated in this case, the onset of the girl's illness at the very time the mother became contagious, together with the course of the illness and the roentgenographic findings, speak strongly in favor of the diagnosis of tuberculosis.

Case 11. The patient (B. V. A.) was a housewife who was born in 1900. There was no family history of tuberculosis. In 1918 the patient had had inflammation of the lung and empyema which was treated surgically. She had never had a chest roentgenogram or been tuberculin tested. Her husband was a tuberculin reactor but had no roentgenographic evidence of tuberculosis. Her son and daughter-in-law were tuberculin negative.

In 1947, roentgenographic examination revealed a right-sided obliteration of the costodiaphragmatic sinus, pleural thickening, apical fibrosis with calcification extending to the third rib, and bronchiectasis. In the left middle field there were partly confluent, coarse-spotted, indistinctly outlined parenchymatous foci. The erythrocyte sedimentation rate

was persistently raised. In 1948 the lesion on the left side progressed, but the patient refused sanatorium treatment; thereafter the illness during the period of observation remained essentially stationary. The patient was in good general condition and was working full time.

Bacteriologic examination: Tubercle bacilli could not be demonstrated in 5 direct sputum samples. In February 1948 culture and guinea pig inoculation of the stomach washings were negative for *M. tuberculosis*.

Tuberculin reactions: In February and in April 1948 and in January 1949 there was no cutaneous reaction to 1.0 mg. of OT.

BCG vaccination: In June 1949 the patient was vaccinated with BCG and there was neither early nor late local reaction. In December 1949 and in June 1950 Mantoux tests with 1 mg. of OT were negative.

Comment

The above 11 cases include 6 patients with unequivocal tuberculosis, 2 with almost certain tuberculosis, and 3 in whom the presence of active tuberculosis is considered to be highly probable. All 11 patients failed to react to the intracutaneous injection of 1 to 3 mg. of OT. The series consists of 7 males and 4 females. All the males were in the age group of thirty to forty years, with one exception who was fifty-nine years of age. The females were all approximately fifty years of age, with the exception of a twelve-year-old girl.

In 8 of the cases the diagnosis of active tuberculosis was verified through repeated positive findings of acid-fast microorganisms, presumably tubercle bacilli. Moreover, in 6 of the 8 patients, cultures were positive for *M. tuberculosis* on Löwenstein medium and in 5, by guinea pig inoculation.

It is naturally regrettable that the bacteriologic diagnosis in all 8 patients with acid-fast bacilli in direct sputum samples has not been confirmed by guinea pig inoculation. In one case (Case 8, acid-fast bacilli in direct sputum sample, cavity), stomach washings and guinea pig inoculation were inadvertently not carried out until the patient had been treated with artificial pneumothorax for three months with good collapse, and the examinations at that time were negative. The other patient refused to permit stomach washings.

In 3 cases (Cases 9, 10, and 11), *M. tuberculosis* could not be demonstrated at all in direct sputum samples, culture, or in guinea pig inoculations. In all 3 of these patients, however, the case histories, together with the clinical and roentgenographic findings and the course of the illness, fully justified the diagnosis of active tuberculosis.

In 2 cases (Cases 2 and 6, both with positive guinea pig inoculations) investigation was made with the thought in mind of a possible coexisting Besnier-Boeck-Schaumann's disease (sarcoidosis), a suspicion which in those 2 cases seemed strongly justified. In both instances, however, the investigations were without positive results. It is generally believed, however, that when tuberculosis complicates sarcoidosis, the tuberculin reaction, as a rule, becomes positive.

BCG Vaccination

Eight of the patients were vaccinated with BCG, 2 of them according to Ustvedt's method of a diagnostic BCG test (37). The Ustvedt technique used is as follows:

A drop of BCG vaccine containing 20 mg. bacilli per cc. was applied to a few scarifications in the skin, after which it was noted whether a local papule developed in the course of the first six days ("early reaction") or appeared for the first time only after some weeks ("late reaction"). Early reaction, according to Ustvedt's and Aanonsen's (37) work, favors the suspicion that the individual examined harbors a tuberculous focus ("those who, in spite of tuberculin-negativity harbor a living tuberculous infection").

Neither of the patients tested in this manner (Cases 1 and 5) showed the slightest local reaction, and on testing three months later they were still tuberculin negative. Of the 6 who were BCG vaccinated intracutaneously in the usual way, 2 became tuberculin positive with a typical papule at the site of vaccination. The 4 others remained negative (one of them even after revaccination). Three of them showed not the slightest local reaction at the site of vaccination. In one patient (Case 10) a local erythema developed four days after BCG vaccination (early reaction?). The erythema blanched in the course of some days and after approximately five weeks a distinct local papule developed.

Apart from these 2 patients who became positive reactors after BCG vaccination, one patient (Case 8) became positive spontaneously after having been a negative reactor for a period of observation of one and one-half years, and one (Case 5) became positive after, or on account of, vaccination of the skin with virulent bacilli and in association with a tuberculid. Nevertheless, two months later he again was negative to 1 mg. of OT. The other cases have thus far remained negative during a period of observation of one to two years in 2 cases, two to three years in 3 cases, and four years in one case. The patient of Case 6 has thus far been observed for only approximately six months. Singularly enough, this case was *once* during the period of observation distinctly positive to 1 mg. (negative to 0.1 mg.) while the reaction five and two months previously and one and two months later was completely negative up to 3 mg. of OT. There is no satisfactory explanation of this phenomenon. A technical error in the performance of the reaction can never be completely excluded. In any case, nothing in the patient's clinical condition could be found which could explain the fact observed.

General Reactive Capacity of the Skin

Bearing in mind the observations of Pilcher (27), Parodi (24), Seeberg (31), and other writers concerning the significance of the power of reaction of the skin on the result of intradermal tests, special investigations have been performed in 7 of the cases with this in view. Passive dermographism was found to be normally present in the 4 patients who were examined for this phenomenon. The rate of absorption of a wheal produced by 0.1 cc. of physiologic sodium chloride was measured in 6 patients. It was found to be more than sixty minutes in 3 cases and forty-five minutes in 3 cases, i.e., normal. Three of the patients reacted normally with the distinct formation of induration on intracutaneous injection of a nonspecific agent, namely, 0.1 cc. of codein solution,

1:1,000. One patient showed normal erythema formation on radiation with a quartz lamp. Thus, in none of the 7 patients who were especially examined was there any evidence of abnormality in the reaction of the skin.

Tuberculin Production of Strain of M. Tuberculosis Isolated from One Patient

The strain of *M. tuberculosis* isolated from the patient of Case 5 was studied to see whether it was in any way peculiar in respect to its capacity to induce tuberculin sensitivity. A guinea pig, injected intraperitoneally with this strain of tubercle bacilli, became tuberculin positive five weeks after infection. In this connection it should be noted that the patient's two children, who can reasonably be supposed to have been infected by him, were both tuberculin positive.

In further studies, a number of tuberculins from this patient's strain of *M. tuberculosis* were prepared in the state bacteriologic laboratory (Dr. L. Silverstolpe).

Old Tuberculin was prepared in the usual way by culturing the bacilli on Sauton's synthetic medium, followed by sterilization and filtration, ultrafiltration, and tenfold concentration of the broth. In addition, a purified protein derivative from Sauton's and one from Dorset's synthetic medium were prepared as well as a raw tuberculin from each solution. In the last-named preparation, only sterilization and filtering off of the bacilli were carried out without concentration by evaporation or ultrafiltration.

The patient (Case 5) failed to react to any of these five tuberculins prepared from his own bacilli. In contrast, 9 tuberculin-positive persons all reacted to 0.01 mg. of the OT thus prepared. Moreover, the 9 persons also reacted to the purified protein derivative prepared from the bacilli of this patient (Case 5). In every instance the reactions were of approximately the same intensity as the reactions to 0.01 mg. of our usual OT which was injected simultaneously.

Vaccination with Human-Virulent Bacilli

Because Ustvedt's diagnostic BCG test gave neither an early nor a late reaction in this patient, an attempt was made to render him tuberculin sensitive by direct vaccination of his skin with his own strain of bacilli taken from a Löwenstein culture. It had previously been established that this strain was pathogenic for guinea pigs.

In 1937 Kutschera v. Aichenbergen (16) reported a study of similar repeated skin vaccinations with virulent bacilli with a therapeutic aim in view. In a patient suffering from tuberculosis the vaccination produces a slight tuberculosis of the skin which it was hoped would produce an improved state of immunity and increased tendency to healing. In 1940 the present writer treated 10 presumably hopeless cases of tuberculosis with this "skin vaccination," according to the reported technique, but discontinued the experiments as no substantial results were apparent. Köhler (15) in 1949, however, published good results with the method applied in approximately fifty cases.

In this tuberculin nonreactor (Case 5), the vaccination resulted in the same

way as is seen in tuberculin-positive patients. Approximately three weeks after vaccination, superficial, brownish-red tuberculides of the skin developed at the site of inoculation without accompanying lymphadenitis or systemic symptoms. It is worthy of note, however, that the patient's reaction to tuberculin, which for more than one year had remained negative up to 3 mg. (despite BCG vaccination and residence in a sanatorium with all its possibilities for superinfection), four months after "homologous" vaccination became positive to 0.1 mg. of OT. Two months later, however, the patient reacted negatively up to 1 mg. of OT, as he had done before vaccination with his own bacilli.

Examination of Serum for Tuberculin-Neutralizing Factor

A series of experiments was made with the aim of possible demonstration of some tuberculin-neutralising factor in the serum of those patients with tuberculin-negative tuberculosis.

Experiments of this type were published in 1908 by Pickert and Löwenstein (25). They examined the serum of "tuberculous persons who displayed a resistance to large doses of tuberculin," i.e., patients suffering from tuberculosis who were desensitized until they could tolerate subcutaneous injection of at least 100 mg. of tuberculin without reaction. They found that such a serum "possessed the power of neutralising or diminishing the specific effect of tuberculin on the skin of tuberculous subjects." Normal serum has, according to these writers, no tuberculin-neutralizing properties. Such agents directed against the specific action of tuberculin were called "anticutins," in contrast to "procutins," i.e., agents considered to augment the effect of tuberculin on the skin. A number of subsequent investigations (Bessau (2), Fernbach (5), and others) yielded very contradictory results. As a consequence, a certain silence fell on these "cutins," until Pinner, Weiss, and Cohen (28) in 1943, almost embarrassed to have to occupy themselves "with the long abandoned theory concerning humoral antibodies in tuberculosis," again took up the question. The occasion for this was that Jadassohn (11, 12) and Martenstein (22) had reported several cases in which they had demonstrated "anticutins" as the cause of the negative tuberculin reaction in sarcoidosis. Jadassohn had also established that anticutins were found in the serum of rats, and demonstrated at the same time that the histopathologic changes which arose after infection of rats with *M. tuberculosis* resembled to a great extent those found in sarcoidosis. Pinner and his co-workers found "so-called anticutins" in approximately 5 per cent of normal or tuberculous sera, and "procutins" in nearly one-half of all those examined. They also found that the presence or absence of "cutins" had no connection whatsoever with the immunologic status of the cases of tuberculosis examined. Moreover, in 8 cases of sarcoidosis they were able to demonstrate anticutins in only one, while in 4 cases they found procutins. In the serum of rats they could not demonstrate any anticutins at all. Likewise, Hamel (6) in 1930 was unable to find any connection between anti- and pro-cutins and the origin of the samples examined. The latter were more common than the former but were evenly distributed among healthy and markedly allergic patients and patients with sarcoidosis or lupus pernio. In

1949 Wells and Wylie (38), however, found in 63 tests with serum from 11 definite cases of sarcoidosis a factor which completely neutralized tuberculin in 52 of the tests and which weakened the reaction by 50 per cent in 7 tests. In only 4 of the tests were no such effects demonstrable. Moreover, they established that this factor was thermolabile. In one case, by electrophoretic fractioning they established that the neutralizing factor was found only in the gamma-globulin, a component of the serum which is usually elevated in sarcoidosis. Finally, Sterling (33) in 1950 reported that in 3 of 4 patients with erythema nodosum and bilateral hilar lymph node enlargement, who showed negative tuberculin reactions, he had been able to demonstrate the presence of a tuberculin-neutralizing factor. Control examination of 2 cases of erythema nodosum with positive tuberculin reactions did not show such a substance.

These extremely interesting, but apparently far from conclusive, investigations led the writer to examine some of these tuberculin-negative patients with active tuberculosis for the presence of a tuberculin-neutralizing factor in the serum. Apparently, such cases have not hitherto been examined from this standpoint. The previous studies have been concerned with sera from: tuberculin-positive healthy subjects; tuberculin-negative, noninfected, newly born infants (Pinner); tuberculin-positive or "desensitized" tuberculous patients; and patients with definite or suspected sarcoidosis.

In the present study the method of Wells and Wylie was used with only slight modification. In sarcoidosis this method has given the majority of positive results. The modification consisted of the fact that the sera were not filtered through a Berkefeld filter. Old Tuberculin was thus diluted with serum from the patient in question, so that 0.1 cc. of serum contained, respectively, 1, 0.1, or 0.01 mg. of tuberculin. The solution was allowed to remain at room temperature for forty-eight hours for "incubation," and was thereafter ready for use. The test was performed as with an ordinary Mantoux by intracutaneous injection of 0.1 cc. At the same time, 0.1 cc. of a corresponding dilution of OT with physiologic sodium chloride solution was injected at another site, and as a further control 0.1 cc. of serum alone was injected, also at a separate site.

The experiments were performed in a guinea pig with serum from Case 5 and in fourteen human volunteers with sera from Cases 5, 3, 9, and 6. The tuberculin-sodium chloride dilution was injected on one arm and the tuberculin-serum dilution, together with the serum control, on the other arm. The results may be seen in the table.

As may be seen in the table, an undoubted tuberculin-neutralizing effect was present in the serum of Case 5. The effect was demonstrated both in a guinea pig and in three human volunteers. In Cases 3 and 6, such an effect of the sera was not demonstrated in tests on four subjects; the two remaining tests cannot be assessed as the serum control also turned out positive. The serum from Case 9 exhibited a tuberculin-neutralizing effect in two healthy volunteers and in one patient with pulmonary tuberculosis; but no such effect could be found using the same OT serum in 2 other patients with pulmonary tuberculosis. All 3 pa-

TABLE 1

Investigations for the Presence of "Anticutins"

SERUM DONOR	RECIPIENT SUBJECT	OT USED	OT – NaCl	OT — SERUM	SERUM CONTROL
		mg.			
Case 5	Guinea pig (6 weeks after inoculation)	1.0	Positive (vesicle)	Negative	Negative
	Volunteer W.M. (Tuberculin positive, healthy)	0.01	Positive (12 x 15 mm.)	Negative	Negative
	Volunteer G.K. (Tuberculin positive, pulmonary tuberculosis)	0.01	Positive (17 x 17 mm.)	Negative	Negative
	Volunteer S.H. (Tuberculin positive, pulmonary tuberculosis)	0.01	Positive (12 x 12 mm.)	Negative (5 x 3 mm.)	Negative
Case 3	Volunteer R. G. (Tuberculin positive, healthy)	0.01	Positive (15 x 15 mm.)	Positive (15 x 15 mm.)	Negative
	Volunteer M. S. (Tuberculin positive, pulmonary tuberculosis)	0.01	Positive (15 x 15 mm.)	Positive (10 x 12 mm.)	Negative
Case 6	Volunteer L. S. (Tuberculin positive, healthy)	0.01	Positive (10 x 10 mm.)	Positive (10 x 10 mm.)	Negative
	Volunteer G. L. (Tuberculin positive, healthy)	0.01	Positive (12 x 12 mm.)	Positive (15 x 15 mm.)	Negative
	Volunteer E. K. (Tuberculin positive, pulmonary tuberculosis)	0.01	Positive (15 x 15 mm.)	Positive (15 x 15 mm.)	10 x 12 mm.
	Volunteer I. S. (Tuberculin positive, pulmonary tuberculosis)	0.01	Positive (15 x 17 mm.)	Positive (12 x 12 mm.)	10 x 10 mm.
Case 9	Volunteer A. B. (Tuberculin positive, healthy)	0.01	Positive (10 x 10 mm.)	Negative	Negative
	Volunteer M. B. E. (Tuberculin positive; after BCG vaccination, healthy)	0.01	Negative	Negative	Negative
		1.0	Positive (12 x 10 mm.)	Negative	Negative
	Volunteer G. E. (Tuberculin positive, pulmonary tuberculosis)	0.01	Positive (10 x 10 mm.)	Positive (10 x 15 mm.)	Negative

TABLE 1—*Concluded*

SERUM DONOR	RECIPIENT SUBJECT	OT USED	OT—NaCl	OT—SERUM	SERUM CONTROL
		mg.			
	Volunteer G. L. (Tuberculin positive, pulmonary tuberculosis)	0.01	Positive (10 x 10 mm.)	Negative (erythema 4 x 5 mm.)*	Negative
	Volunteer E. W. (Tuberculin positive, pulmonary tuberculosis)	0.01	Negative	Negative	Negative
		1.0	Positive (10 x 12 mm.)	Positive (10 x 10 mm.)	Negative

* In all other cases, the area of involvement measured represents induration.

tients had tuberculosis in an active state and had been only recently admitted to the sanatorium.

Thus, the results with the method used here are not conclusive. At the utmost they seem to support the supposition that a tuberculin-neutralizing factor *can* be found, but they provide no convincing support for the notion that this factor is the cause of the negative tuberculin reaction in these cases.

It is believed, however, that this question is of such interest that a more extensive investigation of the problem has been started on a larger scale. Hence, it may be mentioned at this time that of two persons (nursing staff) who, despite repeated BCG vaccination, remained tuberculin negative, "anticutins" could be demonstrated in only one. In one patient with sarcoidosis whose serum was tested according to the same method, complete tuberculin neutralization was demonstrable in one volunteer, partial neutralization of the tuberculin reaction in another volunteer, and in a third volunteer the serum control was positive.

SUMMARY

Eleven patients with roentgenographic findings considered to be characteristic of pulmonary tuberculosis failed to react cutaneously to the intradermal injection of 1 to 3 mg. of tuberculin. All 11 patients were in good general condition and were free from complicating infections.

The presence of tuberculosis was established in 6 of the patients by the isolation of *M. tuberculosis* by culture of sputum. In 2 patients, acid-fast bacilli were seen on microscopic examination of the sputum, but tubercle bacilli were not isolated by culture. In the remaining 3 patients, the bacteriologic examinations for tubercle bacilli were negative.

Six of the patients were vaccinated with BCG; 2 became tuberculin reactors with a local papule after vaccination; one remained a tuberculin nonreactor but showed a possible "early reaction"; 3 showed no local reaction whatsoever and remained nonreactors to tuberculin. In an additional 2 patients, Ustvedt's diagnostic tuberculin test resulted in neither early nor late reactions.

No reduction of the power of reaction of the skin could be demonstrated in these cases as judged by tests with codein as a nonspecific irritant, the rate of

absorption of a sodium chloride wheal, development of erythema after irradiation, and the incidence of passive dermographism.

Four of the patients were investigated for the presence of a tuberculin-neutralizing factor in the serum (so-called anticutin). In one case, the presence of such an anticutin was demonstrated in the serum by tests in a guinea pigs and in three human volunteers. Serum from another case appeared to contain "anticutins" when tested in three of the volunteers but not in another two persons. Sera from the remaining two cases were negative for "anticutins" when tested in six human volunteers.

The strain of *M. tuberculosis* (human type) isolated from one of the patients was studied in detail. A guinea pig became tuberculin positive after inoculation with the strain. Vaccination of the patient's skin with the strain resulted in the development of cutaneous tuberculides without lymph node or general reactions as in tuberculin-positive tuberculous patients. Old Tuberculin and purified protein derivative prepared from the strain caused positive tuberculin reactions in control individuals of the same intensity as those developing by simultaneous testing with ordinary Old Tuberculin.

SUMARIO

Tuberculosis Tuberculino-Negativa

Once enfermos con hallazgos roentgenográficos considerados como típicos de tuberculosis pulmonar no reaccionaron cutáneamente a la inyección intradérmica de 1 a 3 mg. de tuberculina. Los 11 se hallaban en buen estado general y sin complicationes infecciosas.

La presencia de tuberculosis fué establecida en 6 de los sujetos por el aislamiento del *M. tuberculosis* por cultivo del esputo. En 2, observáronse bacilos ácidorresistentes al examinar microscópicamente el esputo, pero no se aislaron bacilos tuberculosos por cultivo. En los otros 3, los exámenes bacteriológicos en busca de bacilos tuberculosos resultaron negativos.

Seis de los enfermos fueron vacunados con BCG; 2 se volvieron reactores a la tuberculina mostrando una pápula local después de la vacunación; uno continuó siendo negativo a la tuberculina, mas reveló una posible "reacción temprana"; 3 no revelaron la menor reacción local y permanecieron negativos a la tuberculina. En otros 2 enfermos, la prueba tuberculínica diagnóstica de Ustvedt no motivó reacciones ni tempranas ni tardías.

En estos casos, no pudo descubrirse disminución de la facultad reactora de la piel, juzgando por pruebas con codeína como sustancia irritante anespecífica, por la velocidad de la absorción de una flictena producida con cloruro de sodio, por la producción de eritema consecutivo a la irradiación y por la incidencia de dermografía pasiva.

Cuatro de los pacientes fueron investigados con respecto a la presencia en el suero de un factor tuberculino-neutralizante (la llamada anticutina). En un caso, la presencia de dicha anticutina fué descubierta en el suero por medio de pruebas en un cobayo y en tres voluntarios humanos. El suero de otro enfermo parecía contener "anticutinas" al ser comprobado en tres de los voluntarios,

pero no en otras dos personas. Los sueros de los otros dos casos resultaron negativos para "anticutinas" al ser comprobados en seis voluntarios humanos.

La cepa de *M. tuberculosis* (tipo humano) aislada de uno de los enfermos fué estudiada con detenimiento. Un cobayo se volvió tuberculino-positivo después de inocularle la misma. La vacunación cutánea del enfermo con la cepa dió por resultado formación de tubercúlides sin reacciones ganglionares o generales como sucede en los tuberculosos tuberculino-positivos. La tuberculina antigua y el derivado proteínico purificado (PPD) preparados de la cepa ocasionaron en testigos humanos tuberculino-reacciones positivas de la misma intensidad que las producidas mediante la comprobación simultánea con tuberculina antigua corriente.

RESUME

Tuberculose avec réaction négative à la tuberculine

Chez onze malades, présentant des images radiologiques considérées comme caractéristiques d'une tuberculose pulmonaire, la réaction cutanée à l'injection intradermique de 1 à 3 mg. de tuberculine a été négative. Ces malades avaient un bon état général et ne présentaient pas d'infection secondaire.

La présence de la tuberculose a été établie chez 6 de ces malades par isolement de *M. tuberculosis* dans les cultures de crachats. Chez 2 malades, des bacilles acido-résistants ont été vus à l'examen microscopique des crachats mais le bacille tuberculeux n'a pas été isolé dans les cultures. Chez les 3 autres malades les examens bactériologiques pour la recherche du bacille tuberculeux ont été négatifs.

Six de ces malades ont été vaccinés par le BCG; chez 2 d'entre eux le tuberculin-test a été positif, une papule locale a été observée à la suite de la vaccination; 1 est resté anergique, toutefois il s'est produit des signes pouvant être interprétés comme un "réaction precoce"; chez 3 malades aucune réaction locale quelqu'elle soit n'a été observée et ils sont demeurés anergiques à la tuberculine. Chez 2 autres malades le tuberculin-test, selon la méthode d'Ustvedt, n'a permis d'observer aucune réaction précoce ou tardive.

Dans ces cas aucune diminution du pouvoir de réaction de la peau n'a pu être mise en évidence par les tests cutanés: codéine comme irritant non spécifique, vitesse de résorption d'une papule de chlorure de sodium, développement d'un érythème après une irradition et la présence de dermographisme passif.

Chez quatre des malades la présence dans le sérum du facteur neutralisant la tuberculine (dit "anticutine") a été recherchée. Dans un cas la présence de ce facteur a été démontrée dans le sérum par des tests sur le cobaye et sur trois sujets qui ont servi de témoins volontaires. Dans un autre cas le, sérum a paru contenir cette "anticutine" quand il a été expérimenté chez trois des témoins voluntaires et non chez deux autres personnes. Le sérum de ces deux derniers cas s'est montré négatif quant aux "anticutines" quand il a été expérimenté chez six témoins volontaires.

La souche de *M. tuberculosis* (type humain) isolée chez un des malades a été étudiée en détail. Un cobaye a été tuberculinisé par inoculation avec cette

souche. La vaccination de la peau du malade avec cette souche a provoqué l'apparition de tuberculides cutanées sans ganglions et sans réaction générale, comme on le voit chez les tuberculeux présentant une réaction positive à la tuberculine. La vieille tuberculine et un dérivé protéique purifié, préparé à partir de cette souche, ont déterminé chez les témoins des réactions positives à la tuberculine. Ces réactions ont été aussi intenses que celles qui se sont manifestées au cours de tests simultanés pratiqués avec la vieille tuberculine ordinaire.

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CUTANEOUS INOCULATION TUBERCULOSIS[1,2]

A Review of the Literature and a Report of Eight Cases

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INTRODUCTION

Physicians and others who work with the sick or recently deceased can contract tuberculosis by skin inoculation. Most of these medical workers are not sufficiently aware of this potential danger to themselves. Moreover, discussion of the most effective methods of treatment has not been widely disseminated. A general review of the most effective methods for the treatment of inoculation tuberculosis has not been presented in over two decades, and notable advances in the therapy of other forms of tuberculosis have occurred during this period. These methods are not necessarily new. In fact, one of the most efficacious, surgical excision of the diseased tissue, was successfully utilized twenty-five years ago. Accordingly, a comprehensive review of past recorded treatments for cutaneous inoculation tuberculosis has been prepared and is presented along with detailed recent case histories. It is hoped that the analyses and conclusions drawn from this study may prove to be of assistance in choosing the best possible treatment for this disease.

Review of the Literature

In 1925, Stokes (29) found 70 cases of cutaneous inoculation tuberculosis which had been reported in the literature. Of these, 58 were reported to have involvement of regional nodes. Forty-one were infections of wounds after ritual circumcisions. In nine cases it was specifically stated that no spread to the nodes had occurred, and in three cases no mention of lymphatic involvement was made.

Stokes also described ten cases studied at the Mayo Clinic. Five of these were cheek inoculations with associated pre-auricular or cervical nodes; two were inoculations of the great toe with subsequent development of groin abscesses; and three were lesions of the upper extremity with draining axillary sinuses. One patient had generalized metastatic carcinoma and was not treated for tuberculosis. In each of the other nine cases, the lesions responded to various types of treatment and healed eventually. A cheek lesion with nonfluctuant regional nodes in one patient was apparently healed after rest, ultraviolet light, and neoarsphenamine. Seven patients were successfully treated by combining surgical excision or incision and curettement with X-ray therapy. One was treated only by radiation of a draining sinus. The behavior of the disease in the inoculation lesions in two of Stokes' patients is worthy of consideration. In these two cases, the epithelialized inoculation sites were not treated until after the involved regional nodes had been excised.

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In each of these cases, in the same regional area there was a recurrence which responded to X-ray therapy after the primary focus had been excised. Tubercle bacilli were demonstrated in the excised scars. Stokes accordingly advised wide excision of the primary focus whenever possible, even if it were only a scar. He also concluded that excision of the secondary nodes whenever possible was the best treatment for the disease.

Michelson (25) in 1935 described two cases. One patient had an ulcer of the forefinger which healed in seven months without treatment. The other had an ankle lesion with inguinal tuberculous adenitis. He was treated by incision and drainage of the ankle abscess, application of a cast to the ankle, and ultraviolet and X-ray therapy to the groin. Healing of both lesions occurred in nine months.

Fidler (22) in 1937 reported the case of a 25-year-old white male who had inoculated his thumb with tuberculous material. Fever, lymphangitis, and axillary adenitis followed. The thumb lesion epithelialized after two months. The axillary mass and the lymphangitis persisted. The primary lesion was widely excised and the lymphangitis and adenitis began to regress. Three months later, a caseous axillary node was removed. The patient showed no further evidence of disease.

O'Leary and Harrison (19) in 1941 reported twelve cases of inoculation tuberculosis of the skin. Surgery combined with X-ray therapy was used in three cases. Eight patients were treated with X-ray alone. The results were good with both types of treatment and in every case the lesions healed within a few months.

Bass (6) in 1946 reported the treatment of a wound of the face (lateral to the eye) made by a splinter from a barn door hit with shell fragments. The injured area was infected with tuberculosis and the cervical nodes became involved. The largest nodes of the neck and the primary ulcer of the face were removed. Postoperatively, the patient was given X-ray and ultraviolet therapy. Healing was prompt.

In 1945 Epstein (9) reported a fatal case of a 64-year-old female who had had a primary tuberculous pulmonary lesion which was known to be healed. She developed an inoculation tuberculous ulcer of her lower lip with extension to neck, lung, breast, and kidney. Treatment with X-ray therapy, rest, tuberculin, and ultraviolet light was given. In discussion of Epstein's paper, Cannon reported successful treatment by excision of the primary lesions of the skin and of involved nodes in two patients who were inoculated with tubercle bacilli in the forefinger and wrist, respectively. Dennis, in discussing the same paper, reported a case of a primary tuberculous complex arising from a fresh tattoo of the arm, followed by miliary spread. The patient was treated conservatively with two years of hospitalization and was apparently well. Twenty years later he experienced a recurrence of tuberculosis in the axillary nodes originally involved.

Weichsel and Salgado (7) in 1946 reported two cases: One was that of a 7-year-old Puerto Rican male who had received an inoculation on the inner inferior aspect of the thigh and subsequently developed a groin abscess. Five months later, both lesions were excised and healing was by first intention. The second case was that of an 8-year-old white female who had had an inoculation of her forehead and subsequently developed a preauricular mass. She was found to have active pulmonary tuberculosis and was hospitalized fourteen months for her pulmonary disease. After eight months, both the pre-auricular mass and the forehead lesion were excised. The wounds healed without difficulty and remained healed.

A laboratory technician who had sustained a known tuberculous inoculation of the skin reported that the development of disease had been prevented by immediate action (34). In 1942, at Middlesex County Sanatorium, Massachusetts, this technician, while assisting at an autopsy on a person known to have had tuberculosis, punctured her left third

finger with a needle. The wound was immediately cauterized deeply with phenol crystals applied with a wooden applicator. In spite of the fact that her skin reaction to tuberculin had been negative a year previously, she had no difficulty with the wound other than a minor phenol burn and a few embedded splinters which were subsequently removed.

CASE REPORTS

Case 1. A 30-year-old white physician, a Resident in Pathology, was admitted to Lawson VA Hospital on September 13, 1948. On August 12 and August 23, 1948, he had performed autopsies on two known cases of pulmonary tuberculosis. In the first case, the patient had had one course of streptomycin (1.0 gm. daily for 120 days from October 24, 1947 to February 20, 1948). No streptomycin had been used in the second case.

On September 2, 1948, the physician observed a papule on the dorsum of the left hand in the web between the first and second metacarpals. By October 8, 1948, a few slightly tender hazel-nut-sized left axillary nodes were present. On October 10, a drop of pus was expressed while he was scrubbing his hands with a brush. The following day chilly sensations, sweats, and fever (100°F.) developed. On October 12, 1948, acid-fast bacilli were found in smears from the lesion on the hand. Past history revealed that the physician had had a one plus skin reaction to first strength PPD in February 1948. A roentgenogram of the chest obtained at the onset of the present illness showed three small parenchymal healed lesions, presumably tuberculous, in the left upper lobe. Cultures from the hand yielded tubercle bacilli which were completely resistant to streptomycin in a concentration of 100 γ per ml. and which were inhibited at a concentration of 250 γ per ml. The erythrocyte sedimentation rate (Wintrobe) on admission to the hospital was 44 mm. per hour and the total leukocyte count was 10,000 per cu. mm., with normal differential. During the first two months of hospitalization, the patient's temperature varied from 98.8° to 99.6°F., in spite of bed rest. A slight, cordlike, tender thickening developed for several centimeters, radiating down the arm along the brachial artery and inferiorly along the lateral chest wall. For local rest, a shoulder spica cast with a window in the axilla was applied on November 15, 1948. The size of the lesion which involved the axillary nodes progressed and the latter were intermittently acutely tender. On November 27, 1948, it was noted that the skin had become red and was fixed to the underlying matted mass of nodes, the size of a hen's egg. Thereafter, fluctuation gradually developed. The abscess was aspirated by needle puncture through superior normal skin at five- to seven-day intervals, and 30, 18, and 8 cc. of pus were withdrawn on those occasions. Tubercle bacilli were demonstrated by smear and culture from the fluids.

The character of the lesion changed very little. After December 1, 1948, the temperature curve was normal, with only 0.5°F. elevations every three to four days. By this time, the erythrocyte sedimentation rate was usually about 25 mm. per hour. On January 8, 1949, the skin over the abscess ruptured and spontaneous drainage occurred. Thereafter, there was intermittent drainage.

Operation: On January 18, 1949, under sodium pentothal and nitrous oxide anesthesia, the lesion on the hand was excised by cautery. At the same time, a partial axillary dissection with complete removal of the involved nodes and involved skin was done. The wound was irrigated with a solution containing 1.0 gm. of streptomycin. The patient was given para-aminosalicylic acid for forty-eight hours preoperatively, and administration of this drug was continued for eight days postoperatively. The dosage was 2.0 gm. orally every four hours. Penicillin was also used until the wounds healed. Postoperatively, the wounds healed without complication. The patient has had no further evidence of disease and can use the involved extremity freely. He was most recently observed in February 1951.

Case 2. A 28-year-old white physician, a Resident in Pathology, was admitted to the Lawson VA Hospital on February 26, 1948, with an indolent ulcer of his left forefinger which had been diagnosed as tuberculous after examination of biopsy material. Early in Decem-

ber he had performed an autopsy on a tuberculous patient, during which he had not been aware of any injury. A month later he developed a cellulitis of the left forefinger. This was subsequently incised for drainage on six different occasions. He received a single injection of penicillin in oil, and twelve days later developed urticaria and joint effusion, which disappeared following Pyribenzamine therapy. Three weeks after the appearance of the finger lesion, a biopsy was taken and the material was histologically tuberculosis. In the latter part of January 1948, the patient was given streptomycin, 0.5 gm. daily, for two weeks and one gm. daily for eleven days. The size of the lesion on the finger had decreased 50 per cent. He was then transferred to Lawson VA Hospital for further treatment.

The patient gave no personal, family, or contact history of tuberculosis except that of his profession. His skin reaction to tuberculin (first-strength PPD) was four plus in January 1948. He had had no systemic symptoms, nor evidence of spread of the disease beyond the local lesions. At the time of admission to Lawson VA Hospital, an ulcer with surrounding soft tissue swelling of the palmar surface was noted overlaying the terminal interphalangeal joint of the left index finger. A roentgenogram of the finger showed no evidence of bone involvement. A roentgenogram of the chest showed calcified scars adjacent to the right hilum, but no evidence of active pulmonary tuberculosis. The erythrocyte sedimentation rate was 17 mm. per hour (Wintrobe); the total leukocyte count was 8,500 per cu. mm., with 30 per cent lymphocytes. The patient was afebrile and remained so throughout his hospitalization.

The streptomycin therapy was continued in dosage of 0.5 gm. every twelve hours until he had been treated with the drug for a total of four months. In addition, the lesion was treated with quartz light therapy. On June 2, 1948, chemotherapy was discontinued. Although the ulcer had changed very little, the surrounding swelling had decreased. The patient was discharged from the hospital to be followed as an outpatient. A communication from the patient received in April 1949 stated that, although the ulcer had completely healed, movement of the distal joints of the finger was definitely limited.

The following case is one of regional tuberculous adenitis in which cutaneous inoculation was not definitely established.

Case 3. A 37-year-old white minister was admitted to Lawson VA Hospital on December 12, 1948 complaining of pain and nodular swelling in his left axilla. He first noted a small tender "kernel" in this region three weeks prior to admission. Enlargement, redness, and heat followed. The patient had anorexia, general malaise, sweats, feverish sensations, and had lost ten pounds in weight. At the age of fourteen years he had had an abscess in the left axilla, which after incision drained continuously for three months before it healed. With the same episode, he had several furuncles scattered over his body. There was no history of pulmonary tuberculosis or of exposure to tuberculosis.

At the time of admission the nodes of the left axilla were enlarged, firm, matted, tender, and fixed to the overlying reddened skin in one minute area. No other nodes were palpable. The total leukocyte count was 11,750 per cu. mm., with 24 per cent lymphocytes, the erythrocyte sedimentation rate was 48 mm. per hour (Wintrobe).

Hot packs were applied to the involved area for the relief of pain. The patient ran a low-grade fever with daily elevation to 100°F. A week after admission, the axillary mass became fluctuant. At the same time, tender supraclavicular nodes, tender lymphatic vessels extending retrogradely along the brachial artery and inferiorly along the lateral chest wall, were noted. Creamy yellow pus was aspirated from the axillary mass on three separate occasions. It was examined by smear, culture, and animal inoculation for various microorganisms, including fungi and tubercle bacilli. All reports were negative. On January 11, 1949, seven days after the first aspiration, there was spontaneous breakdown of the skin with drainage of pus through the site of a needle puncture. Drainage persisted for six days only and ceased spontaneously. At the same time, the supraclavicular nodes began to regress in size. On February 6, 1949, nine days after the drainage ceased, a node was excised

from the axilla. The histologic picture of the node was that of tuberculosis, although no acid-fast bacilli were found. The biopsy wound healed without difficulty.

On February 7, 1949 the patient was given streptomycin, 0.5 gm. every twelve hours. Continued regression of all nodes followed. After fourteen days of this therapy, his lymph nodes were no longer palpable. The patient's temperature elevation persisted for only two weeks after admission to the hospital. His erythrocyte sedimentation rate was normal at the time he was given streptomycin and remained so until the time of discharge from the hospital.

Case 4 (The Norburn Hospital and Clinic, Asheville, North Carolina (36)). A 14-year-old Negro male student was first seen at the Norburn Hospital on July 19, 1948, complaining of a mass growing on his right foot. This mass was first noted eighteen months previously and had recently begun to grow rapidly, although specific injury was unknown. Several enlarged painful nodes had appeared in his right groin after the lesion was noted on the right sole. One of these nodes ruptured spontaneously and drained purulent material for an indefinite period, but was not draining at the time of the initial examination. The mass on the foot was excised. The report on the tissue on the basis of histologic pattern and positive acid-fast stains was cutaneous tuberculosis.

The operative wound on the inner surface of the right sole healed without difficulty. On July 28, 1948, a scar over the site of previous drainage and several large nodes (one fluctuant) were present in the right groin. At that time, a chest roentgenogram was negative for tuberculosis although the patient was underweight and seemed to be chronically ill.

He was observed as an outpatient and treated with streptomycin (1 gm. intramuscularly daily for six weeks). Soon after this treatment was begun the patient's appetite increased and he gained weight. The nodes in the groin decreased in size and he felt better. By October 9, 1949, he had gained four pounds and his temperature was normal. His general appearance improved. The groin nodes were smaller and were neither tender nor fluctuant. The patient was dismissed. No evidence of this disease was reported in a letter written February 12, 1949.

Case 5 (The Norburn Hospital and Clinic, Asheville, North Carolina (36)). This was a case of a 26-year-old white physician, a Resident in Pathology at Duke Hospital, Durham, North Carolina. On March 23, 1941, while performing an autopsy on a patient (diagnosis unknown), he superficially scratched his right wrist. He immediately washed the scratch with alcohol. On April 26, 1941, the patient noted a painful enlarged pea-sized, right epitrochlear node. Three days later, his total leukocyte count was 7,500 per cu. mm. and the differential was normal. A papule at the site of the original scratch was seen on April 30, 1941. At this time the epitrochlear node had enlarged slightly and was moderately tender, and the patient had a degree (F.) of evening temperature elevation. On May 2, 1941, the papule ulcerated. Two days later a cold cellulitis appeared around the epitrochlear node which was now almond sized. The lymphatic chain to the axilla became tender without local reddening and two small tender axillary nodes were observed.

The patient entered the hospital on May 5, 1941. Agglutinations for tularemia, brucella, sheep's erythrocytes, and the Wassermann test were negative. Routine cultures and smears from the ulcer were negative. In spite of the use of saline packs to the ulcer for two days and local dry heat for another day, the ulcer continued to enlarge and deepen. On May 8, 1941, a skin reaction to tuberculin OT was 3 plus in dilution of 1:1,000. Before this sickness, the patient had had a negative skin reaction to tuberculin and a chest roentgenogram which was negative for tuberculosis. On May 9, 1941, the chest roentgenogram was again negative. During the next eleven days the muscles of the entire right arm were sore, a soreness which was relieved by acetylsalicylic acid. On June 5, 1941, microscopic specimens from the body autopsied by the patient were studied, and the diagnosis was miliary tuberculosis.

The patient returned to work on July 6, 1941, feeling better. Although the epitrochlear node was still enlarged and tender, it was smaller and firmer. Three days after returning

to work he developed fever, and the soreness in his arm increased. During the next few weeks he lost ten pounds. He was hospitalized and transferred from Duke Hospital to the Western North Carolina Sanatorium where he was placed on partial bed rest until November 13, 1941. During this time, all use of the involved area was prevented, although the primary wrist ulcer had healed in July 1941. He was given a series of deep X-ray treatments over the involved epitrochlear and axillary nodes. The patient was on a high vitamin (especially vitamin D), high caloric, and high calcium intake. In October 1942, he went to Georgia State Sanatorium (Alto, Georgia) where he began working part time. Nine months later, occasional soreness of the right arm was still present, occurring about twice a month and accompanied by about one-half degree of evening temperature elevation. Therapy with X-ray was continued until two full courses, given to tolerance, had been completed.

On October 17, 1942, the patient had infectious mononucleosis. A febrile course ensued, and the patient was hospitalized for two and one-half weeks with fever slightly over 100°F. The symptoms in the arm were markedly increased during this period, although there was no recurrence of fluctuation or drainage. Thereafter, he continued part- and full-time work at the Georgia State Sanatorium, using his left arm for the greater part of his activity. Pain in the epitrochlear nodes persisted, and occasionally slight soreness in the axillary nodes was noted. A cast was applied to the right arm but was worn only for two weeks, with no benefit noted. Low-grade afternoon fever persisted.

Operation: In 1943, surgical removal of the affected epitrochlear nodes was done under local anesthesia. After the nodes were removed, the lymph chains on each side were cauterized with phenol. The incision drained in three areas for three weeks and then healed uneventfully. Sections from the nodes were reported as tuberculous granulation tissue with caseation necrosis and occasional giant cells, although no tubercle bacilli were demonstrated.

After the surgical excision of the epitrochlear nodes, the patient continued to have soreness of the arm and febrile reactions several times a month. Accordingly, desensitization with tuberculin was attempted. His skin reaction was now found to be positive to OT in a dilution of 1 to 100,000. The procedure of desensitization was begun with 0.1 cc. of OT diluted one to one million. The dose was doubled each day, but the patient began to get local reactions. After a rest period of several weeks, treatment was begun again, using 0.1 cc. of the dilution one to ten million, and increasing 0.1 cc. daily. When the dilution of one to one million was reached, the patient began to get both local and systemic reactions, so this therapy was abandoned.

After the treatment was stopped, he improved gradually. He has been working regularly since 1944. During 1944 and 1945, he had a few low-grade febrile reactions. Up to June 20, 1949, no definite activity of the disease showed itself, although occasionally there is definite soreness above the right elbow. No masses, however, have been found.

Case 6 (The North Carolina Sanatorium for the Treatment of Tuberculosis, McCain, North Carolina (37)). A physician at the North Carolina Sanatorium for the Treatment of Tuberculosis reported that by accidental rotation of a curved needle used for sewing up the body of a patient who had died of pulmonary tuberculosis he had penetrated his contaminated glove and made a slight scratch on the skin of the right thumb. A small tubercle developed about September 10, 1948. Three weeks later, a brawny induration and cellulitis appeared in the arm and extended on to the palmar surface of the thumb. The tubercle developed a small ulceration from which tubercle bacilli were recovered on October 16, 1948. Two subsequent efforts to culture tubercle bacilli from the lesion were unsuccessful. Streptomycin was given for thirty days, beginning October 7. The strain of *M. tuberculosis* proved sensitive to streptomycin at a concentration below 10 γ per ml. The ulcer healed about November 10. The finger was immobilized for approximately six weeks and protected in its range of activity for six months. No serious results followed except a marked limitation of extension of the first digit. No adenitis in the axilla or at the elbow was observed.

Case 7 (The Paterson General Hospital, Paterson, New Jersey (39)). A 30-year-old male physician, Resident in Pathology, was hospitalized on October 26, 1946, complaining of pain and tenderness in his right axilla. Twelve days previously, he had first noted a non-painful swelling on the right index finger, which was incised but no pus was found. Continuous wet dressings were used on the finger for two days and the patient returned to his usual activities. No particular change was noted until October 23, when right axillary adenopathy was discovered. The axilla became progressively painful and malaise developed. At the time of hospital admission malaise had increased and temperature was 102°F. The patient was known to have had a positive skin reaction to tuberculin for several years. Examination on admission showed that the right axilla contained several enlarged, firm, tender, discrete nodes, the largest of which was 2 cm. in diameter. Tender, enlarged nodes were also found in the left axilla, which were smaller and less tender than those on the right. A culture from the right index finger yielded a mixed growth of *Streptococcus* with a nonhemolytic variety in predominance.

The patient was treated by continuous hot soaks to the entire right upper extremity, by penicillin intramuscularly, and by sulfadiazine orally. The temperature and pulse gradually returned to normal. The lesion of the right forefinger healed and the axillary nodes subsided. A papule on the ulnar surface of the left wrist remained. The time of the first appearance of this papule was not recorded. On December 23, 1946, the papule and surrounding skin on the ulnar aspect of the left wrist were removed. The papule was approximately 1 cm. in diameter and extended into the subjacent tissue for approximately 0.5 cm. Pathologic diagnosis was tuberculoma of the skin. The sections were reviewed by several pathologists and all concurred in the diagnosis.

The patient was admitted to Veterans Administration Hospital, Bronx, New York, in April 1949 with bilateral minimal pulmonary tuberculosis. There was no residual evidence of the lesion of the wrist except the scar made by the excision.

Case 8 (VA Hospital, Bronx, New York (39)). A male physician, a Resident in Pathology, while performing an autopsy on a tuberculous patient (October 17, 1948) lacerated his left thumb. About three weeks later he developed a red swollen area near the interphalangeal joint. This area was slightly tender, and shortly developed superficial fluctuation, followed by spontaneous discharge of a drop of thin pus which showed acid-fast bacilli on smear. There was no evidence of lymphangitis or of lymphadenitis, and no involvement of the bone was seen in the roentgenogram of the thumb. The patient had been exposed to a tuberculous parent in childhood and was known to have been a cutaneous reactor to tuberculin since the age of ten. Roentgenograms of his chest taken since 1940 showed an old bilateral apical infiltrate which had never given rise to symptoms.

The patient was advised to immobilize the thumb and was told that no further treatment would probably be necessary. He was followed for a month by the consulting dermatologists and then went to Florida for a vacation. Because of the indolent character of the lesion, it was treated with a few applications of Grenz ray in January 1949. The patient stated that the lesion "melted away" immediately thereafter.

He was re-hospitalized in April 1949 because of a new area of infiltration in the apex of his left lung field. At the time of this admission, gastric washings were positive for tubercle bacilli. The pulmonary lesion was regarded as an extension of his old lesion and was not related to the lesion of his thumb which had remained healed.

DISCUSSION

After tubercle bacilli are inoculated into the skin of man, the ensuing disease follows one of two patterns: The lesion may be localized at the site of inoculation or it may spread. Progression occurs usually by way of the lymphatics to the regional nodes in which inflammation, swelling, caseation, fluctuation, and spon-

taneous drainage may be anticipated. If the lesion remains local because of a previous increase in the defensive power of the host, it all too frequently becomes an indolent ulcer which persists for many months.

The behavior of tuberculosis incurred as a pulmonary infection is similar to that seen after skin inoculation. The mediastinal lymph nodes enlarge greatly with a primary pulmonary infection, but there is no change seen in the nodes when they are in the drainage pathway of a post-primary parenchymal infection. To be sure, exceptions to these rules occur.

Koch demonstrated the difference between a primary and a secondary skin inoculation with tubercle bacilli in the guinea pig. In the animal which had had a previous inoculation or vaccination of this disease, the lesion was confined to the site of introduction; but in a susceptible animal the disease spread to the regional nodes and frequently entered the blood stream. Generally speaking, these patterns may be transposed to man. Nevertheless, there are patients whose second infection behaves like a primary infection. This is illustrated in 2 of the cases presented in this paper and in the case described by Epstein.

In Case 1 the expected course in a known tuberculin reactor with chest roentgenograms revealing an old Ghon complex was localization of the disease to the site of the inoculation. In spite of this, there was a spread to the regional nodes. The patient of Case 7 behaved in the same exceptional manner (known previous tuberculin reactor). In Case 5 (known previous tuberculin nonreactor with no roentgenographic evidence of pulmonary disease), one would have anticipated involvement of neighboring nodes, as was found to occur. Cases 2, 6, and 8, in each of which it was presumed that the patient had cutaneous hypersensitivity to tuberculin at the time of his skin inoculation, had no spread of disease beyond the local inoculation ulcers.

If it be presumed that tuberculosis has the same basic behavior in different parts of the body, observations made in the treatment of pulmonary tuberculosis and in the treatment of cervical tuberculous adenitis have bearing on the problem of the treatment of skin inoculation disease. It is well recognized that caseous pulmonary lesions may resist all types of medical therapy while surgical excision of a lobe or lung containing a lesion of this type may be the road to health for the patient. In a similar way, caseous tuberculous nodes in the neck may be most completely and quickly eradicated by excision (1, 33, 35). If tuberculosis is being treated in any part of the body, the thought of the use of chemotherapy in conjunction with surgical excision must be kept in mind. There is always a danger that if chemotherapy is used as a primary agent for therapy, a drug-resistant infection may appear if the agent is used for too long. Accordingly, the optimal time for adjunct surgery may be missed.

To evaluate various methods of treatment, the completeness of cure, the speed of cure, and the least possible residual side effects must be compared. Each of the types of therapy, however, is probably best suited to different phases of the disease.

The review of the literature and two of the cases reported in this paper suggest that surgical excision of tuberculous disease usually results in a prompt cure

of the disease. This method of treatment may prevent protraction of the disease (Case 5). If the cutaneous lesion and the involved lymph nodes are discrete and small, complete and immediate removal is the quickest and surest method of cure. If the patient has never had streptomycin therapy or if the infecting organisms are not streptomycin resistant, a short course either of streptomycin or of one of the newer antituberculous drugs, together with such general measures as good nutrition, general rest for fever and fatigue, and local rest of the involved part, are indicated. During the time that chemotherapy is being given, it is wise to excise the inoculation ulcer.

X-ray therapy has had general acceptance as a method of treatment per se and as an adjunct to other methods. It increases the fibrous reaction around the lesion and encourages healing by the formation of scar tissue. X-ray therapy is, however, ineffective in caseous or abscessed glands. Indeed, it encourages abscess formation in lymph nodes which are approaching liquefaction. It is recognized that some internists experienced in the field of tuberculosis are very much opposed to the use of such therapy for the treatment of tuberculous lymph nodes in the neck. This position is assumed because of the fact that occasionally one sees patients with miliary tuberculosis who have recently had deep X-ray therapy for cervical nodes. On the other hand, it is also true that in adult patients with miliary tuberculosis enlarged superficial lymph nodes are not at all uncommon. As a consequence, the existence of a causal relationship between X-ray therapy and the development of miliary tuberculosis has not been established with certainty.

If either extensive caseation or liquefaction is present, it is unlikely that antimicrobial therapy could be effective because of the avascularity of the mass of necrotic tissue and other factors. Complete walling off of the lesion by scar formation or by its spontaneous evacuation would require many months for completion. Such diseased tissue should either be removed by excision or evacuated by incision and curettage. All surgical procedures except the simplest incision and drainage should be delayed until the systemic reaction in the patient has subsided and until his general condition is good. Streptomycin is beneficial in the preparation of the patient for surgery and in the assurance of good postoperative results.

SUMMARY

Persons who work with tuberculosis are always in danger of contracting the disease through skin inoculation.

Cutaneous inoculation tuberculosis, with or without regional adenitis, usually will respond well either to a conservative medical regimen or to surgical excision of the diseased tissue.

X-ray therapy to the involved areas will aid in healing, if there is no evidence of fluctuation in the lesion.

Streptomycin or other antituberculous drugs, either alone or in conjunction with surgery, are helpful in healing the disease.

Incision and curettement of fluctuant nodes may be beneficial as a preliminary or final treatment of a particular area of disease.

Complete surgical excision of the skin lesion and of all other diseased tissue is the most rapid and satisfactory method for the treatment of patients with cutaneous inoculation tuberculosis.

SUMARIO

Tuberculosis por Inoculación Cutánea: Repaso de la Literatura y Presentación de Ocho Casos

Los que trabajan con tuberculosis corren siempre el peligro de contraer la dolencia mediante la inoculación cutánea.

La tuberculosis por inoculación cutánea, con o sin adenitis regional, responderá por lo general bien ya a un régimen médico conservador o a la excisión quirúrgica del tejido afectado.

La roentgenoterapia aplicada a las zonas afectadas ayudará la curación, sino hay fluctuación ganglionar declarada o cercana.

La estreptomicina u otras drogas antituberculosas, ya solas o unidas a la cirugía, son útiles en la curación de la enfermedad.

La incisión y el curetaje de los ganglios fluctuantes pueden resultar beneficiosos como tratamiento preliminar o final de una zona enferma dada.

La completa excisión quirúrgica de la lesión cutánea y de todo el demás tejido enfermo constituye el método más rápido y completo para curar al paciente.

RESUME

Inoculation cutanée de la tuberculose: Une revue de la littérature et un rapport sur huit cas.

Le danger de contracter la tuberculose par inoculation cutanée existe pour ceux qui effectuent des travaux en tuberculose.

Les lésions tuberculeuses cutanées par inoculation, avec ou sans adénite régionale, répondent habituellement de façon satisfaisante au traitement médical ou à l'excision chirurgicale des tissus affectés.

La radiothérapie de la région intéressée facilite la guérison, en l'absence de fluctuation véritable ou imminente.

La streptomycine ou toute autre médication antituberculeuse, soit seule soit en association avec l'acte chirurgical, favorise la guérison de la maladie.

L'incision et le curetage des ganglions fluctuants peuvent se montrer utiles comme traitement préliminaire ou définitif d'une localisation particulière de la maladie.

L'excision chirurgicale radicale de la lésion cutanée et des autres tissus affectés constitue le moyen le plus rapide et le plus complet pour guérir le malade.

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STUDIES ON THE COMMUNICABILITY OF HISTOPLASMOSIS[1,2]

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INTRODUCTION

The concept that there is a widespread but benign form of histoplasmosis is receiving growing acceptance. However, only a few tentative strides have been made toward the solution of the epidemiologic problem which this hypothesis poses. Little is known concerning the modes of spread and the communicability of histoplasmosis in man or animals.

The concept that the excessive pulmonary calcifications seen in the Middle West are at least partially the result of a widespread benign form of histoplasmosis has not been fully substantiated. The basis for this hypothesis rests on indirect evidence, namely: (*1*) pulmonary calcifications, many of which occur in tuberculin-negative persons, are more numerous in the Middle West than in any other section of the country; (*2*) the incidence of histoplasmin skin reactors is higher in this same area than in any other part of the country; and (*3*) the Middle West is the endemic center of the reported cases of histoplasmosis. The demonstration of the causative fungus, *Histoplasma capsulatum*, in the pulmonary nodules of histoplasmin-positive individuals has been rarely accomplished.

A variety of researches have been conducted not only in man but also in domestic and wild animals and in soil because the sources and modes of spread of histoplasmosis are not known. Emmons (1) states: "Whether the exposure of man to animals with histoplasmosis is important in the epidemiology of human histoplasmosis is a question of considerable importance. Unfortunately, we are unable to answer it at the present time." Emmons (2) recently was able to recover *H. capsulatum* from samples of soil. The fungus has been found in rats and skunks (3), mice and cats (4), dogs (5), and a Kodiack bear from the Columbus, Ohio, zoo (6).

De Monbreun (5) was the first to recognize the disease in the dog and suggested that it might be transmitted from dogs to man. He demonstrated that *H. capsulatum* recovered from the dog is culturally and morphologically the same as the organism causing histoplasmosis in man. Since that time others have considered the dog as a possible source of the disease in man, among them Pará (7), who reported histoplasmosis in a child and in a closely associated dog in the same household. Olson, Bell, and Emmons (4) investigated the relationship of 3 dogs with naturally occurring histoplasmosis to 4 reported human cases in Loudon County, Virginia. They were unable to demonstrate any association between the dogs and the human patients. Ticks, *Dermacentor variabilis*, were

[1] From the Department of Medicine, and the Department of Veterinary Pathology, Ohio State University, Columbus, Ohio.

[2] Project supported jointly by Comly Fund, College of Medicine, and The Veterinary Pathology Research Fund.

allowed to feed on one of the dogs ill with histoplasmosis, and soon after this blood meal *H. capsulatum* was recovered from the ticks.

As reported previously, 1,314 dogs were skin tested with histoplasmin in this laboratory, only 7 of which showed a positive reaction (8). In 4 of the 7 histoplasmin reactors the presence of clinically active histoplasmosis was established by culture, by demonstration of *H. capsulatum* in the tissues, or both. Since the above report was completed, 896 additional dogs have been tested, making a total of 2,210. Of this total number, 18 dogs have shown skin reactions to histoplasmin. Twelve of these 18 dogs have been found to have active histoplasmosis. The diagnosis was established by culture of *H. capsulatum* from tissues or body fluids of 9 and was demonstrated microscopically in the lesions of 10 animals. The number of cases of naturally occurring histoplasmosis in dogs in central Ohio is larger than that reported from any other area. Although the incidence of histoplasmin reactors in dogs is quite low (0.94 per cent), the percentage of the reactors with active histoplasmosis is very high (66.6 per cent).

In distinct contrast to these findings was the incidence of histoplasmin reactors (66.5 per cent) found in university students residing in the same central Ohio area (9). Pulmonary calcifications were seen in 17.0 per cent of this same group. It is of interest to note that among the more than 18,000 students studied, only 2 have been found to be clinically ill with histoplasmosis.

The finding of considerable histoplasmosis in dogs which were household pets in a region of high incidence of histoplasmin reactivity in man suggested that the dog might serve as a possible source of the infection. This was especially true in those who had prolonged exposure to these animals. Thus, it was decided to study for evidence of histoplasmosis the humans exposed to dogs with naturally occurring disease.

OBSERVATIONS

In order to determine the communicability of histoplasmosis in animals, the present study included dogs shown to be free of histoplasmosis which were kept in cages adjacent to those with infected animals.

Careful pathologic study of 11 dogs with naturally occurring histoplasmosis has been made to determine the various means by which *H. capsulatum* might be eliminated from dogs and thus infect other animals or human beings (10). These studies show that there are at least four potential routes of dissemination of the fungus from dogs:

1. The finding of *H. capsulatum* in the tracheal and bronchial exudate, bronchial nodes and in the lungs suggests that *sputum* may be a source of infection.
2. Ulcerative and proliferative lesions containing *H. capsulatum* in the mouth, esophagus, and stomach suggests the possible elimination of the fungus from the upper digestive tract by *saliva* or *vomitus*.
3. Extensive enterocolitis was a common finding. In some dogs the organism can be demonstrated in the expelled *feces* as well as in the intestinal lesions.
4. Granulomatous lesions that contained *H. capsulatum* were found in wall of the bladder and in the kidneys. Thus, *urine* can be a source of infection.

In addition it has been suggested that canine ectoparasites may possibly serve as a source of infection.

Experimental Procedure

Of the 12 dogs with naturally occurring histoplasmosis, 7 were household pets. There were 25 people who lived in intimate contact with these animals during the active phase of their histoplasmosis. The exposure ranged from two to four months. In addition, there were 8 laboratory workers who examined, cared for, handled, and disposed of excreta and performed necropsies on the same dogs. These same workers performed essentially the same services on 9 other dogs with artificially induced histoplasmosis. This intimate contact varied from two months to one year. A complete physical examination was given to the members of each group, a histoplasmin skin test was applied, and blood was drawn for histoplasmosis complement fixation and collodion agglutination tests. Chest roentgenograms were available on 26 of the adult human contacts.

Eight dogs with active naturally occurring histoplasmosis were held in an isolation ward for an average period of 7.5 months. The diagnosis of histoplasmosis was established by culture and microscopic demonstration of *H. capsulatum* in one or more of the body tissues or fluids. In another ward, 9 dogs which had been artificially inoculated with the fungus were held in strict isolation.

Five healthy young dogs were used as room-exposure controls. For several months prior to exposure, each of the dogs was given repeated physical examinations and serial blood studies, immunized against canine distemper, and treated for endo- and ecto-parasites. In addition, all dogs had chest roentgenograms and histoplasmin skin tests were applied, to which all failed to react. Complement fixation and collodion agglutination tests for histoplasmosis were performed on the serum of each animal. These 5 healthy dogs were placed in cages adjacent to the 8 dogs with spontaneous histoplasmosis. They were exposed for an average period of 7.5 months. In addition, 2 of the dogs were subsequently exposed to 9 dogs with artificially induced disease. During the period of exposure, the control dogs were subjected to repeated physical and hematologic examinations, chest roentgenograms, serologic studies, and histoplasmin skin tests.

A two-year-old Pointer from a kennel of 6 dogs was found to have active histoplasmosis. The 5 dogs naturally exposed to the infected dog were all examined and histoplasmin skin tests were applied.

RESULTS

Studies in dogs: A two-year-old male Pointer dog, having had a persistent nonproductive cough for six weeks reacted to the histoplasmin test. Pulmonary nodules were observed in chest roentgenograms, and *H. capsulatum* was found in the feces and cultured from the lungs. Gross and microscopic lesions characteristic of histoplasmosis were found in tissues removed at necropsy. This animal had been in a kennel with 5 other dogs. The 5 other dogs living and playing together in the same kennel appeared to be healthy in all respects and failed to

react to histoplasmin. Although the dog affected with histoplasmosis was eliminating *H. capsulatum* in the feces, no evidence was found to suggest that transmission to the other dogs in the kennel had occurred.

Five healthy histoplasmin-negative dogs were placed in the isolation room in cages adjacent to those occupied by the dogs with naturally occurring histoplasmosis. Three of the 5 room-control dogs developed positive histoplasmin skin reactions. *H. capsulatum* was demonstrated in the lesions of 2 of the animals, and gross and microscopic lesions typical of histoplasmosis were observed in the third animal. These findings tend to confirm the previous studies concerning the value of the histoplasmin skin test in the detection of active canine histoplasmosis (8).

The first dog (No. 50-68) developed a positive histoplasmin reaction after exposure of two months to the 8 dogs having spontaneous histoplasmosis. Pulmonary lesions became evident on chest roentgenograms and *H. capsulatum* was cultured from the lung biopsy.

The second dog (No. 50-338) was insensitive to histoplasmin in December 1949 and in January 1950. However, a positive skin reaction was elicited for the first time in April 1950. In this case, skin reactivity developed after a period of four months' exposure to 8 dogs with spontaneous histoplasmosis. Chest roentgenograms revealed peripheral pulmonary nodules, and following necropsy *H. capsulatum* was demonstrated in the lungs and bronchial lymph nodes.

The third dog (No. 50-98) developed a histoplasmin reaction after five months of exposure to the 8 dogs with spontaneous histoplasmosis. The skin test was negative in December 1949 and in January 1950. Since the dog was not retested until June 1950, when a positive reaction was elicited, it is not known exactly when the skin reactivity first developed. Roentgenograms of the chest showed pulmonary infiltrates and enlarged hilar nodes, and at necropsy multiple nodules, 1 to 3 mm. in diameter, were found scattered throughout all lobes of both lungs. Similar lesions were found in the gastrointestinal tract and renal cortex. Microscopically, these lesions were identical with those found in other dogs with active histoplasmosis, although the fungus was not seen.

No evidence of histoplasmosis has been found in the fourth and fifth dogs which subsequently have been exposed to 9 dogs with artificially induced histoplasmosis. The period of exposure to experimental disease was seven months and four and one-half months, respectively. Repeated studies have shown no evidence of histoplasmosis.

Studies of human contacts: In each instance, the human household contacts proclaimed themselves to be in good health, and physical examination failed to reveal evidence suggestive of active histoplasmosis. Of the 25 household contacts tested with histoplasmin, 16 showed the presence of a definite skin reaction after forty-eight hours (table 1). There were no histoplasmin reactors among the 4 children tested. Of the 5 adults who failed to react, 2 were 16- and 17-year-old males who were life-long residents of Columbus, Ohio; one was a 29-year-old female who had been in Columbus only three years, having resided in

TABLE 1

Human Household Contacts of Dogs with Proved Active Histoplasmosis

INITIALS	AGE	SEX	HISTOPLASMIN REACTION IN MM.	COMPLEMENT FIXATION	COLLODION AGGLUTINATION	RESIDENCE	OBSERVED SIGNS IN DOGS WITH ACTIVE HISTOPLASMOSIS
	years						
1. J. P.	68	M	35 × 50	0	0	Born Wisconsin; in Columbus, Ohio since 1920	Fox terrier, 2 years, female. Coughing and wheezing, at times causing vomiting, three to four months.
2. E. P.	63	F	32 × 44	0	0	Lifetime resident of Columbus, Ohio	
3. E. S.	27	F	34 × 40	Weakly plus 1:10		Lifetime resident of Columbus, Ohio	
4. S. S.	32	M	26 × 40	0	0	Lifetime resident of Columbus, Ohio	
5. J. S.	1½	F	0	0	0	Lifetime resident of Columbus, Ohio	
6. G. S.	3	F	0	0	0	Lifetime resident of Columbus, Ohio	
7. J. C.	16	M	22 × 40	0	0	Lifetime resident of Columbus, Ohio	
8. L. C.	23	M	14 × 20	Weakly plus 1:10	0	Lifetime resident of Columbus, Ohio	English sheep dog, female, 1½ years. Admitted because of intractable cough of two months' duration.
9. J. C.	19	F	15 × 22	0	0	Lifetime resident of Columbus, Ohio	
10. N. C.	17	M	0	0	0	Lifetime resident of Columbus, Ohio	
11. D. C.	16	M	0	0	0	Lifetime resident of Columbus, Ohio	
12. E. L.	27	M	6 × 10	0	0	Born Rhode Island; resident of Columbus, Ohio since 1946	Springer spaniel, male, 2½ years. Persistent cough for 6 weeks made worse by activity.
13. A. L.	29	F	0	0	0	Born Rhode Island; resident of Columbus, Ohio since 1946	
14. G. L.	3	F	0	0	0	Lifetime resident of Columbus, Ohio	
15. J. G.	70	F	0	0	0	Lifetime resident of Columbus, Ohio	English setter, 14 years, female. Dermatitis and carcinoma of lip; extensive enteritis due to *H. capsulatum*.
16. C. C.	63	M	12 × 21	0	0	Lifetime resident of Columbus, Ohio	Pointer, male, 3 years. Weight loss and diarrhea, occasionally containing blood.
17. J. T.	23	F	44 × 56	0	0	Lifetime resident of Columbus, Ohio	Springer spaniel, female, 9 years. Cough of 6 weeks' duration; increased thirst.
18. R. T.	47	F	12 × 24	0	0	Lifetime resident of Columbus, Ohio	
19. O. T.	51	M	8 × 14	0	0	Lifetime resident of Columbus, Ohio	
20. L. H.	23	F	28 × 40	1:10	0	Lifetime resident of Columbus, Ohio	Scottish terrier, female, 5 years. Cough of 4 months' duration; diarrhea for two months accompanied by ulcers on neck and back.
21. W. H.	31	M	34 × 50	1:5	0	Lifetime resident of Columbus, Ohio	
22. W. H., Jr.	3 months	M	0	0	0	Lifetime resident of Columbus, Ohio	
23. R. G.	20	F	30 × 43	1:10	0	Lifetime resident of Columbus, Ohio	
24. M. G.	56	F	0	0	0	Lifetime resident of Columbus, Ohio	
25. F. A.	33	M	14 × 20	0	0	Lifetime resident of Columbus, Ohio	

Rhode Island the remainder of her life; and the fourth and fifth were 56- and 70-year-old women, both of whom were lifetime residents of central Ohio. The incidence of histoplasmin reactors is little greater than that already reported for residents in central Ohio (9). Chest roentgenograms of 18 adults in this group showed the presence of pulmonary calcifications in 7.

The results of serologic studies, which included complement-fixation and collodion agglutination tests for histoplasmosis, did not reveal evidence suggestive of active disease. All sera from these individuals gave a negative reaction to the collodion agglutination test. Two showed the presence of a weak one plus reaction in 1:10 dilution to the complement-fixation test. It has been the experience of Saslaw (11) that patients with active histoplasmosis will show by his technique for the complement-fixation test a titer of 1:40 or more. It is his opinion

TABLE 2

Laboratory Workers Exposed to Dogs with Naturally Occurring and Artificially Induced Histoplasmosis

INITIALS	AGE	SEX	HISTOPLASMIN SKIN REACTION IN MM.	COMPLEMENT FIXATION	COLLODION AGGLUTINATION	RESIDENCE
	years					
1. C. C.	33	M	12 x 14	Weakly plus 1:20	0	Columbus, Ohio
2. D. C.	27	M	0	0	0	New Hampshire
3. R. C.	28	M	10 x 15	0	0	Columbus, Ohio
4. R. S.	20	M	0	0	0	Ashland, Ohio
5. D. W.	24	M	20 x 30	0	0	Akron, Ohio
6. D. S.	21	M	15 x 25	0	0	Akron, Ohio
7. H. E.	29	F	6 x 8	Weakly plus 1:20	0	Columbus, Ohio
8. J. R.	24	F	0	0	0	New York

that the questionable reactions reported herein do not suggest active histoplasmosis.

The results of similar studies of 8 laboratory workers exposed to both naturally occurring and artificially induced canine histoplasmosis failed to disclose any evidence of active histoplasmosis (table 2). Five of the 8 had postive histoplasmin skin test reactions. It is of interest that 2 of the 3 nonreactors had been residents of eastern states until the past year. The serologic tests in 6 of this group showed no reaction; 2 showed only weak one plus reaction in 1:20 dilution for the complement-fixation test. The collodion agglutination tests were negative in all members of this group. Chest roentgenograms of this group revealed no parenchymal lesions. Only 2 had pulmonary calcifications, both of whom reacted to histoplasmin.

SUMMARY

1. Three of 5 dogs developed histoplasmosis while exposed to 8 dogs with naturally occurring histoplasmosis. Each of the 3 dogs which were histoplasmin

skin test negative before exposure to infected animals developed histoplasmin reactivity within two to five months after exposure began. This finding is in accord with the previous reports indicating the specificity of the histoplasmin skin test in the detection of active canine histoplasmosis.

2. No evidence of histoplasmosis was found in 2 dogs which were exposed to the animals with spontaneous disease as well as to 9 dogs with artificially induced histoplasmosis.

3. Five dogs that lived in a kennel with a dog found to have active histoplasmosis showed no evidence of the disease.

4. In a group of 25 human household contacts of dogs with active histoplasmosis, there was no indication that any had the active disease. Moreover, there was no evidence that any of the 8 laboratory workers had active histoplasmosis as a result of their prolonged exposure to dogs with both naturally occurring and artificially induced histoplasmosis, although 5 showed positive skin reactions.

5. Although no evidence in this study was found suggesting the transmission of canine histoplasmosis to man, its communicability from dog to dog has been established. The possibility still remains that histoplasmosis may be transmitted from animals to man but it has not yet been possible to demonstrate any direct relationship between canine and human histoplasmosis.

6. In spite of the fact that no proof of a causal relationship could be shown to exist between the disease in dogs and man, the dog should be considered a potentially dangerous source of *H. capsulatum* because it has been demonstrated that the fungus can be disseminated via (a) sputum; (b) saliva or vomitus; (c) feces; and (d) urine.

SUMARIO

Estudios sobre la Transmisibilidad de la Histoplasmosis

1. Tres de cinco perros manifestaron histoplasmosis mientras estaban expuestos a ocho perros con histoplasmosis de aparición natural. Los tres perros, que eran cutirreactores negativos a la histoplasmina antes de la exposición a los animales infectados, manifestaron reactividad histoplasmínica en término de dos a cinco meses de la iniciación de la exposición. Este hallazgo concuerda con previas comunicaciones indicativas de la especificidad de la cutirreacción a la histoplasmina en el descubrimiento de histoplasmosis canina activa.

2. No se descubrieron signos de histoplasmosis en dos perros que estuvieron expuestos a los animales con enfermedad espontánea así como a nueve perros que tenían histoplasmosis evocada artificialmente.

3. Cinco perros que vivían en una perrera con un perro en el que se descubrió histoplasmosis activa no revelaron signos de la dolencia.

4. En un grupo de 25 convivientes caseros humanos de perros con histoplasmosis activa, no había indicación de que ninguno tuviera la enfermedad activa. Tampoco había signos de que ninguno de los ocho laboratoristas padeciera de histoplasmosis activa a consecuencia de su prolongada exposición a perros con enfermedad tanto espontánea cuanto provocada artificialmente, aunque cinco mostraron cutirreaciones positivas.

5. Si bien no reveló este estudio datos que indicaran la transmisión de la histoplasmosis canina al hombre, he sido establecida la transmisibilidad del perro al perro. Resta aun la posibilidad de que pueda transmitirse la histoplasmosis de los animales al hombre, pero los AA. no han podido todavía descubrir la menor relación directa entre la histoplasmosis canina y la humana.

6. A pesar de no haberse podido descubrir prueba alguna de relación etiológica entre la enfermedad en los perros y en el hombre, hay que considerar al perro como foco potencialmente peligroso del *H. capsulatum*, por estar demostrado que ese hongo puede ser diseminado por estas vías: (a) esputo; (b) saliva o vómito; (c) heces; y (d) orina.

RESUME

Etudes sur la contagiosité de l'histoplasmose

1. Cinq chiens ont été mis en contact avec huit chiens atteints d'histoplasmose contractée naturellement; trois chiens ont été contaminés. Chez chacun de ces chiens le test cutané à l'histoplasmine s'était montré négatif avant l'exposition à la contagion; la réaction est devenue positive au cours des deux à cinq mois qui ont suivi le début de ce contact. Ce fait est en accord avec les rapports antérieurs qui signalent la spécificité du test cutané à l'histoplasmine pour le diagnostic de l'histoplasmose canine en activité.

2. Aucun signe d'histoplasmose n'a été découvert chez deux chiens en contact avec des animaux atteints d'histoplasmose naturelle et avec neuf chiens atteints d'histoplasmose par inoculation.

3. Cinq chiens qui étaient dans le même chenil qu'un chien atteint d'histoplasmose en activité n'ont présenté aucun des signes de la maladie.

4. Parmi un groupe de 25 personnes habitant dans des maisons où vivaient des chiens atteints d'histoplasmose en activité, aucune manifestation de l'infection n'a été observée. De même, l'examen de huit sujets travaillant dans un laboratoire où ils avaient été exposés de façon prolongée au contact de chiens atteints d'histoplasmose naturelle, ou d'histoplasmose par inoculation, n'a révélé aucun signe d'histoplasmose en activité bien que, chez cinq d'entre eux, la réaction cutanée ait été positive.

5. Bien que cette étude n'ait pas permis de découvrir la preuve d'une transmission de l'histoplasmose canine à l'homme, la contagion de chien à chien a été démontrée. Il est toutefois possible que cette contagion de l'histoplasmose de l'animal à l'homme existe, mais jusqu'à présent nous n'avons pas été en mesure de mettre en évidence une relation directe entre l'histoplasmose humaine et l'histoplasmose canine.

6. En dépit du fait qu'il n'existe pas de preuve d'un rapport de cause à effet entre la maladie chez l'homme et la maladie chez le chien, le chien doit être considéré comme une dangereuse source potentielle de *H. capsulatum* parce qu'il a été démontré que le fongus peut être disséminé par l'intermédiaire des crachats, de la salive ou des matières vomies, des fèces et de l'urine.

Addendum

Since this communication was submitted for publication, 2 additional dogs with active histoplasmosis have been found. There were 3 persons in one family and 4 in the other who

had been in continuous contact with the dogs during the course of their active disease. All 7 were studied, and no evidence of histoplasmosis was found.

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STREPTOKINASE–STREPTODORNASE IN THE TREATMENT OF EXTRAPLEURAL HEMATOMA COMPLICATING EXTRAPLEURAL PNEUMOTHORAX[1]

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INTRODUCTION AND REVIEW OF LITERATURE

The initial enthusiasm for extrapleural pneumonolysis has been considerably dampened during the past years by the many complications with attending mortality and morbidity and by the difficulties of management of the extrapleural space during the immediate postoperative period. Modern transfusion and anesthesia technique has reduced the operative mortality to a very small figure. Bronchopleural and esophagopleural fistulas are being seen less and less frequently, with refinement in the operative technique and with more judicious choice of patients to be subjected to the operation. Extrapleural empyema has become a rare complication chiefly due to the use of preoperative and postoperative parenteral chemotherapy. When empyema does occur, it is usually treated successfully by penicillin and streptomycin lavage of the space.

The progress in the operative and postoperative management of this form of collapse, the greater and greater awareness of the deleterious effects of paradoxical chest wall motion of thoracoplasty, the demonstration of the selectivity and pulmonary function-sparing characteristics of extrapleural pneumothorax (1), and recent reports of large series of extrapleural pneumonolysis with good end results (2, 3, 4) have revived the interest in this operation.

Postoperative bleeding into the extrapleural space is still encountered in spite of meticulous operative technique and apparently good hemostasis at the end of the procedure. Although many of these hematomas undergo spontaneous liquefaction in the immediate postoperative period, frequently clots cause difficulties in management of the space in the immediate and later postoperative period and eventually lead to abandonment of the space. This complication is invited by the very uniqueness of the procedure. Extrapleural pneumothorax is the only operation which has as its aim the creation of a large air-filled dead space lined, at least partially, by denuded tissue surfaces. Extrapleural hematoma has been cited as an important complication in most of the large series reported. Meticulous surgery with electrocoagulation of all bleeding points under direct vision was first advocated by Adelberger (5). This did not suffice to avoid the complication, for sudden bleeding into the space was often noted twenty-four or more hours after surgery (6).

Attempts to forestall and treat the complication of hematoma have been numerous. Schmidt suggested the elimination of the use of procaine with epi-

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[2] Public Health Service Research Fellow of the National Institutes of Health.

nephrine since he believed that the vasoconstrictor action often masked small bleeding points up to the time of surgical closure of the space (6). In spite of this precaution, he recorded extensive hemorrhage into the extrapleural space in 10 per cent of 200 operations. Alarcon, reporting 277 extrapleural operations, mentioned extrapleural hematoma before all other complications (4). He advocated early reoperation for removal of the clot to avoid permanent loss of the space and the appearance of fever, tachycardia, and delirium. Seip recorded his experience with 602 operations and related that a number of spaces became very difficult to manage and were lost because of coagulated blood and fibrin within the space (2). Furthermore, he suggested that such spaces appeared to be more prone to later infection than clean ones. He therefore introduced a regimen which included placement of 300 cc. of 1 per cent sodium citrate solution in the cavity at the time of operation. The fluid was replaced with like amounts of citrate

TABLE 1

Complications Following Extrapleural Pneumonolysis

Forty-three Operations, June 1948 to November 1950

COMPLICATION	NUMBER	PER CENT
Operative deaths	0	0
Late deaths	0	0
Tuberculous empyema	1	2.3
Nontuberculous empyema	0	0
Bronchopleural fistula	0	0
Spread of disease	0	0
Extrapleural bleeding with clot formation	6	13.9
Space abandoned	7	16.3
because of:		
Extrapleural clot	3	7.0
Empyema	1	2.3
Persistent intrapleural-extrapleural communication	1	2.3
Space lost in immediate postoperative period	2	4.6

through a catheter daily for five days. The method resulted in clean extrapleural spaces but profuse, uncontrollable hemorrhage was often encountered, necessitating multiple transfusions and even autotransfusion. Placement of heparin within the space resulted in a fatality. The program was therefore abandoned and troublesome clots and fibrin were once more encountered (2).

The present writers have performed 43 extrapleural operations since 1948 either as a preliminary to a modified thoracoplasty (7) or in patients whose pulmonary reserve did not permit any other collapse procedure (1). Attempts were made to avoid extrapleural clot formation by placing 300 cc. of normal saline solution in the cavity at the end of the operation. In spite of this, late hemorrhage with clot formation was by far the most frequent complication (table 1). Prior to the use of streptokinase-streptodornase, this complication led to the eventual abandonment of the space in 3 patients or 7 per cent of operations (table 1).

The discovery by Tillett and Sherry (8) of the rapid lysis of blood clots and other coagula by purified extracts of hemolytic *Streptococci* has placed a new and powerful therapeutic tool in the hands of the surgeon. Two components, "streptokinase" (SK), a fibrinolysin factor, and "streptodornase" (SD), a nucleoprotein lysin factor, were isolated, purified, and concentrated by Christensen (9). At present these substances are prepared in various combinations from a nonpathogenic Lancefield Group C *Streptococcus* by a somewhat modified method. They are available in the lyophilized state in which they are sterile and stable (10).

Clinically these substances have been found of great value. The SK factor has been made use of chiefly in the treatment of spontaneous, traumatic, and postoperative intrapleural hemothorax (11). Results have been almost invariably good to excellent (10). The SD factor is of greater importance in the treatment of older or contaminated hemothoraces and in acute and chronic empyema. It too is apparently a valuable therapeutic adjunct and its activity is still under investigation (12).

OBSERVATIONS

Method

Use of SK-SD in the treatment of extrapleural hemothorax following extrapleural pneumonolysis has been reserved for patients in whom the coagulum was so extensive as to render the continued maintenance of the space impossible. In 2 of the 3 patients treated, SK-SD became available only some time after the space had been abandoned. One patient had had no thoracentesis for twenty-two days when SK-SD became available. The use of these agents was further reserved for patients in whom it had become clear that no further spontaneous liquefaction of the clots would occur, that is, two weeks or more after operation. In the 3 patients cited the SK-SD mixture was injected sixteen, twenty-four, and forty-three days after operation.

A commercial lyophilized SK-SD mixture was used[3] containing 200,000 units of SK and 200,000 units of SD per ampule. The powder was dissolved in 20 cc. of sterile saline solution immediately prior to use. It was injected in the extrapleural space, usually in the first interspace in the midclavicular line. Proper location of the needle was assured by withdrawal of small clots or fibrin. After injection, patients were placed on a liquid diet. A four-hour temperature chart was started and 0.6 gm. of acetylsalicylic acid was given by mouth every four hours for three days. Roentgenograms of the chest were taken immediately prior to, and twelve and twenty-four hours after, injection. The space was dried by thoracentesis twenty-four hours after injection and was then tapped until it remained dry. All spaces showed complete liquefaction of the clot within twelve hours and all spaces have been clear and clean and were easily maintained by weekly refills of air.

[3] The SK-SD used in this study was supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., through the kindness of Dr. J. M. Ruegsegger.

CASE HISTORIES

Case 1. W. C., a 38-year-old machinist, was admitted to the Boston Sanatorium for the second time after a survey chest film showed active tuberculosis. Another survey film, taken four years previously, had led to his first admission. At that time, all sputum and gastric cultures were negative for *M. tuberculosis*, and the patient was discharged three months later. On the present admission, the roentgenogram showed mottled infiltration of the right upper lobe, with multiple small cavities. The sputum was positive for acid-fast organisms. Three weeks after admission, the patient's treatment was interrupted by an episode of acute reactive depression, necessitating a brief stay at a state psychopathic hospital. On his return the roentgenogram showed further progression, and that trend was not reversed during the next four months of modified bed rest. Extrapleural pneumonolysis therefore was recommended as a preliminary stage to a modified thoracoplasty.

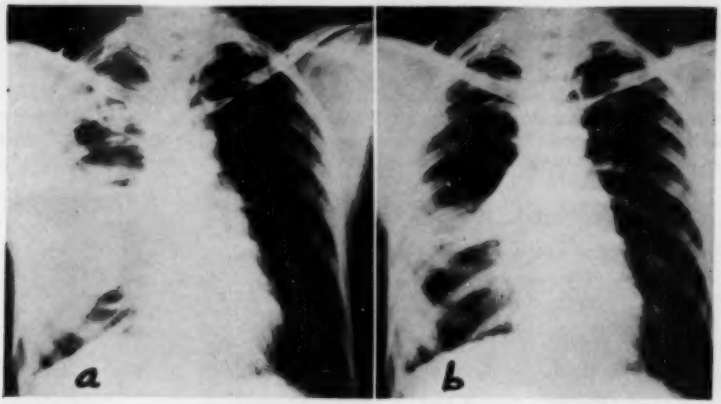
Operation: The operation was unusually difficult and prolonged because of many dense, vascular, apical adhesions. Hemostasis was established only with difficulty. In spite of transfusion of 1,000 cc. of whole blood, the patient's blood pressure on return to the ward was only 80 systolic and 40 diastolic in mm. of mercury, and two further transfusions of 500 cc. were given during the night. A bedside roentgenogram revealed an extrapleural space which was larger than the extent of the operative dissection, and the space was filled with fluid. One gram of streptomycin and 500,000 units of penicillin were injected in the space every day for fourteen days. On the second, third, and fifth days, 150 and 250 cc. of sanguinous fluid were withdrawn from the space, and enough air was injected to bring the pressure just to the positive side. One week after operation no more fluid was obtained on thoracentesis, but the roentgenogram showed many small pockets and loculations with multiple fluid levels. One large adhesion appeared to hold the apex of the lung suspended to the dome of the thoracic cage (figure 1a). The space was then irrigated with saline solution every other day in an attempt to free it of clots and debris. This maneuver proved unsuccessful, and two weeks after operation a remaining small air pocket was found only with difficulty. The injection of a few cubic centimeters of air caused a rapid rise in pressure and it was believed that further refills would be of no avail.

Enzymatic Therapy

On the twenty-fourth postoperative day, 200,000 units of SK-SD dissolved in 20 cc. of saline were injected into the residual air pocket. Three hours after injection the patient began to complain of headache and nausea. That night his temperature rose to 102.6° F. and he began to vomit. Elevated temperatures and vomiting continued for three days (figure 2), and the intravenous infusion of saline solution was necessary on the second and third days. Low-grade fever and anorexia continued for twelve days after the administration of the drug, but appetite and temperature then returned to normal.

Fluoroscopy, twelve hours after injection, showed complete liquefaction of the clot and disappearance of the apical adhesions. During the first two days after injection, 550 cc. of dark brown, oily fluid were removed from the space (figure 2). Roentgenograms revealed an increase in the size of the space, and at one time the floor of the extrapleural space appeared at the level of the diaphragm. An intrapleural effusion was noted at the same time and 100 cc. of straw-colored fluid were removed from this space on the seventh and tenth days after injection. During the ensuing month both the intrapleural and extrapleural spaces remained dry and the extrapleural space was easily maintained by small weekly refills with final pressures just on the positive side (figure 1b).

Case 2. B. S., a 25-year-old mother of two, was admitted to the Boston Sanatorium when a culture of the sputum showed *M. tuberculosis*. Eleven years prior to admission a roentgenogram of the chest had shown minimal infiltration at the apex of the left lung. The patient was not treated and felt well until two years prior to admission when a roentgenogram obtained shortly after a miscarriage showed progression of pulmonary disease. The patient



Case 1

FIG. 1. a. Roentgenogram sixteen days after extrapleural pneumonolysis.
b. Roentgenogram five weeks after injection of SK-SD. The treatment was complicated by a sterile intrapleural effusion.

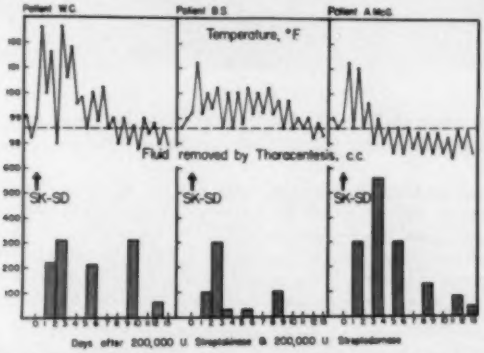


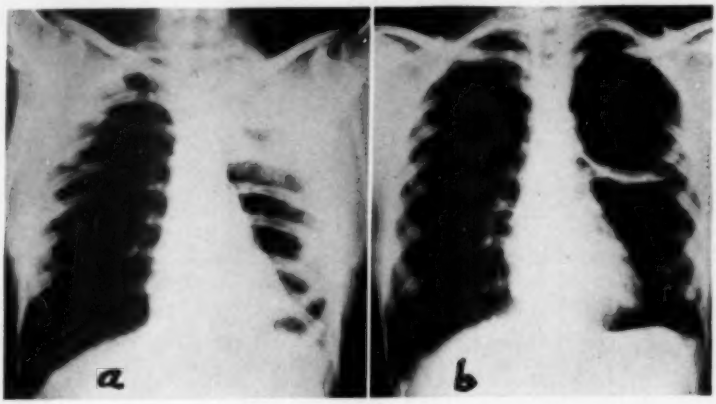
FIG. 2. Temperature charts and fluid removed by thoracentesis from the extrapleural space after injection of SK-SD in 3 patients.

rested at home for three months and then resumed her duties as housewife. She continued to feel well but was persuaded to enter the Sanatorium when a culture was reported positive for *M. tuberculosis*.

On admission, the roentgenogram showed infiltration of the apex of the left lung with a one-centimeter cavity at the level of the first anterior intercostal space. No change was

observed in this lesion during three months of strict bed rest. Several sputum concentrates contained acid-fast organisms.

Operation: Because of the chronicity of the lesion and because of the patient's unwillingness to take prolonged sanatorium care, a left extrapleural pneumonolysis was carried out on the one hundredth hospital day as a preliminary stage to a modified thoracoplasty. The very thin parietal pleura was accidentally opened. Nevertheless, the lung was freed in the extrapleural plane to the desired level and two catheters were introduced, one in the extrapleural space and one in the intrapleural space. Little bleeding was encountered during the operation and the space was dry before closure. The patient received 1 gm. of streptomycin parenterally for fourteen days and 1 gm. of strepromycin and 500,000 units of penicillin were placed in the extrapleural space daily for fourteen days. Both catheters were removed on the second postoperative day, and small amounts of sanguinous fluid were withdrawn from both the intrapleural and extrapleural spaces on several occasions. The first few days after operation, 200 to 400 cc. of air were introduced into the extrapleural space without



Case 2

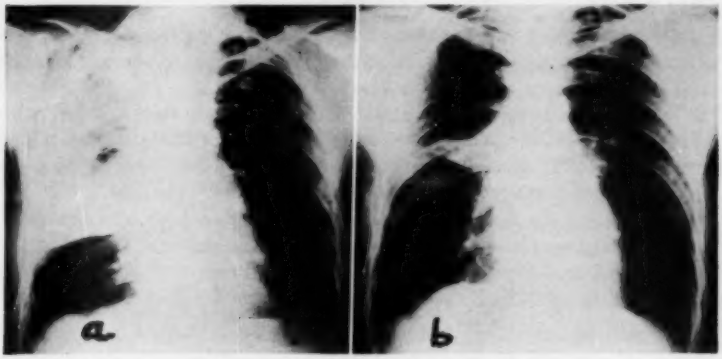
FIG. 3. a. Roentgenogram forty-three days after pneumonolysis.
b. Roentgenogram two months after a single injection of SK-SD.

difficulty and without raising the pressure above +20 cm. of water. After the first week it became more and more difficult to find the space; many small clots were aspirated, and as little as 50 cc. of air raised the pressure to +50 cm. of water or more. The roentgenogram after two weeks showed large clots and loculated spaces with multiple fluid levels. After three weeks there was only a small cap of clotted blood and fluid above the partially re-expanded apex of the lung. It was decided to abandon the space (figure 3a).

Enzymatic Therapy

SK-SD became available on the forty-third postoperative day, two weeks after the last attempt at the introduction of air. Approximately 50 cc. of air were introduced under high pressure into the residual space until fluctuations of the manometer were observed. Twenty cubic centimeters of saline solution containing 200,000 units each of SK and SD were then introduced. Approximately four hours later the patient became quite nauseated and began to vomit. Severe

vomiting continued for three days, necessitating the maintenance of fluid balance by intravenous feeding. Malaise and loss of appetite continued for another week. Urticaria which occurred almost immediately after injection was treated successfully with antihistaminic drugs. The temperature rose to 101.2° F. four hours after injection and returned to normal in twelve days (figure 2). Twenty-four hours after injection, 100 cc. of dark brown fluid were removed and a like amount of air was introduced with a final pressure of +30 cm. of water. More fluid was removed on the second, third, fifth, and eighth days after injection (figure 2). Two weeks after treatment the chest roentgenogram showed a large, clean extrapleural space (figure 3b). This space has been maintained by weekly refills of 100 cc. of air with final pressures of +20 and +30 cm. of water. A small amount of clear yellow fluid was aspirated three weeks after injection, and for the past five months the space has been dry.



Case 3

FIG. 4. a. Roentgenogram twenty-four days after pneumonolysis.
b. Roentgenogram three months after a single SK-SD treatment.

Case 3. A. McG., a 37-year-old, unemployed, chronic alcoholic male, was admitted to the Boston Sanatorium because of fever, night sweats, loss of weight, and a productive cough of three months' duration. A roentgenogram of the chest showed pneumonic infiltration of the upper half of the right lung field and a two-centimeter cavity with fluid level. The sputum was positive for acid-fast bacilli. Three months' bed rest were interrupted by a week-long unauthorized absence from the hospital. On the patient's return, he had mild delirium tremens. The infiltration showed considerable clearing during this time but no change in size of cavity. Bronchoscopy revealed purulent drainage from the right upper lobe orifice.

Operation: Three months after admission, a right extrapleural pneumonolysis was carried out as a preliminary step to a modified thoracoplasty. On the first postoperative day, bleeding into the space occurred. Thoracentesis revealed that the blood had clotted, and no fluid could be withdrawn. Several small air pockets were maintained by daily refills with air and streptomycin-penicillin solution. During the next two weeks only partial liquefaction of the hematoma occurred, and no more than 50 cc. of changed blood were withdrawn on any one day (figure 4a).

Enzymatic Therapy

On the sixteenth postoperative day, 20 cc. of saline solution with 200,000 units SK-SD were injected into a small air pocket. Almost immediately the patient complained of severe right chest and shoulder pain and he developed urticaria. Medication with antihistaminics and meperidine controlled these complaints. Some nausea and evening temperatures up to 101.4° F. persisted until the fourth day after injection (figure 2). During the first five days after injection, 1,150 cc. of a black oily fluid were withdrawn from the extrapleural space (figure 2). The space has remained dry since two weeks after injection and has been easily maintained by weekly refills of 100 cc. of air with a final pressure of +30 cm. of water (figure 4b). Four months after operation, the extrapleural space was converted into a modified thoracoplasty as had been planned.

SUMMARY

Extrapleural hematoma was the most frequent complication in a recent series of 43 extrapleural pneumonolyses. It occurred after six operations and led to the eventual abandonment of three spaces.

The last three clotted spaces were treated sixteen, twenty-four, and forty-three days, respectively, after operation by a single injection of 200,000 units of streptokinase and 200,000 units of streptodornase. Complete liquefaction of the clotted, loculated space occurred within twelve hours in every instance.

Toxic symptoms due to the drug persisted for five to twelve days but were of minor nature and consisted of fever, urticaria, nausea, and vomiting. Continued maintenance of an adequate extrapleural pneumothorax was possible in every case although the space had been previously abandoned in 2 of the 3 patients.

SUMARIO

La Estreptoquinasa-Estreptodornasa en el Tratamiento del Hematoma Extrapleural Complicando el Neumotórax Extrapleural

El hematoma extrapleural constituyó la complicación más frecuente en una reciente serie de 43 neumonolisis extrapleurales, ocurriendo después de seis operaciones y conduciendo al abandono eventual de tres espacios.

Los últimos tres espacios coagulados fueron tratados, a los dieciséis, veinticuatro y cuarenta y tres días, respectivamente, de la operación con una sola inyección de 200,000 unidades de estreptoquinasa y 200,000 unidades de estreptodornasa. En todos los casos sobrevino completa licuación del espacio loculado, coagulado, en término de doce horas.

Por espacio de cinco a doce días persistieron síntomas tóxicos debidos a la droga, pero fueron de importancia secundaria, consistiendo en fiebre, urticaria, náuseas y vómitos. En todos los casos fué posible mantener continuamente un neumotórax extrapleural adecuado, aunque el espacio había sido previamente abandonado en 2 de los 3 enfermos.

RESUME

Streptokinase-Streptodornase dans le traitement de l'hématome extra-pleural compliquant le pneumothorax extra-pleural

L'hématome extra-pleural a été la complication rencontrée le plus fréquemment dans une série de 43 pneumolyses extra-pleurales. Il s'est produit après six interventions et a conduit à l'abandon éventuel de trois espaces.

Les trois derniers espaces où se trouvait le caillot ont été traités respectivement, seize, vingt-quatre et quarante-trois jours après l'intervention par une unique injection de 200.000 unités de streptokinase et de 200.000 unités de streptodornase. Dans chaque cas la liquéfaction totale des caillots a été obtenue en douze heures.

Les symptômes toxiques causés par cette médication ont persisté pendant cinq à douze jours, mais ils étaient peu importants; ils consistaient en fièvre, urticaire, nausées et vomissements. Un pneumothorax extrapleural adéquat a pu êtremaintenu dans chacun des cas, malgré l'abandon antérieur de l'espace chez 2 de ces 3 patients.

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CHEMOTHERAPY OF TUBERCULOSIS[1]

IV. Studies with Sulfones in the Mouse

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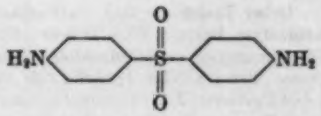
INTRODUCTION

At the time that interest in the sulfonamides as therapeutic agents was at a peak, it was also recognized that certain sulfones showed therapeutic activity. Feinstone, Bliss, Ott, and Long (1) reported that *p,p'*-diaminodiphenylsulfone was more active in experimental streptococcal infections than was sulfanilamide; but in the opinion of the writers its toxicity precluded its use in human beings. The diacetyl derivative of *p,p'*-diaminodiphenylsulfone was reported to be inactive in experimental tuberculosis in guinea pigs by Greey, Boddington, and Little (2).

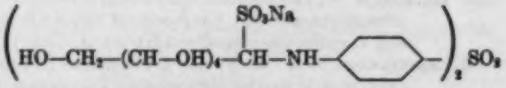
During the years following these early papers, reports of studies with several hundred sulfones have appeared, the chief emphasis being placed on attempts to reduce the toxicity of the parent compound without destroying its therapeutic efficacy. It is not the purpose of the present paper to review this extensive literature, but rather to discuss certain findings concerning the sulfones in experimental tuberculosis in an investigation in which the mouse has been used as the experimental animal.

During the past ten years, the sulfones which have received chief attention have been the following:

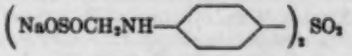
p, p'-diaminodiphenylsulfone



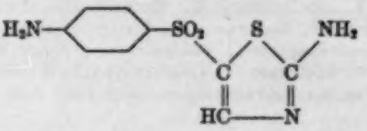
Promin



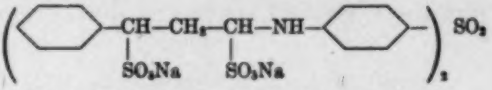
Diasone



Promizole



Sulphetrone



[1] From the Squibb Institute for Medical Research, New Brunswick, New Jersey.

Of these compounds, three are different from *p,p'*-diaminodiphenylsulfone (DDS) only in that substitutions have been made on the two *p*-amino groups. Since Greey and associates (2) had already shown that the diacetyl compound was inactive in the experimental infection in guinea pigs, it was of interest to note that the activity is not necessarily destroyed when substitutions are made on the *p*-amino groupings. Thus, Feldman and his associates (3, 4) were able to demonstrate chemotherapeutic action with Promin, as well as with Diasone (5). Raizias, Clemence, and Friefelder (6) reported that the combination of DDS and sodium formaldehyde sulfoxylate in Diasone was a firm one and was not split by various physiologic agents. When administered by mouth, this compound was said to be less toxic for rabbits and mice than the parent compound, whereas the therapeutic efficacy was said not to be reduced proportionately. Similar claims were made for Sulphetrone by Brownlee and Kennedy (7).

Corper and Cohn (8) also reported activity on the part of Diasone in experimental tuberculosis in the guinea pig when administered *per os*, but not parenterally. These authors stated that this compound had neither a direct bactericidal or bacteriostatic action on the organism (since it showed very low activity *in vitro*), and they concluded that the effect was directly related to the cyanotic effect caused by the compound. They appear to have been unaware at that time that the drug was hydrolyzed when given by mouth (as was later shown to be the case by Titus and Bernstein (9); see below). It is interesting, therefore, to note that Fernandez, Bergel, and Carboni (10), impressed by the importance of the effect of the oxidation-reduction potential of culture medium on the growth of *Mycobacteria*, apparently attributed the cyanosis caused by Diasone to the sodium formaldehyde sulfoxylate contained in this molecule. These authors, therefore, tested the sulfoxylate in a number of cases of leprosy and reported favorable results. Sodium formaldehyde sulfoxylate was also tested by Genu and De Oliveira Lima (11), who reported that no beneficial effects were noted.

There is adequate evidence in the literature to indicate that cyanosis may be caused by oral administration of sulfones other than Diasone, e.g., *vide* Dancy, Schmidt, and Wilkie (12), who carried out studies in man with Promin, and such symptoms need not be attributed to sodium formaldehyde sulfoxylate. Nevertheless, whatever the explanation may be, it is possible to demonstrate a low level of therapeutic action with sodium formaldehyde sulfoxylate in experimental tuberculosis in the mouse. In the writers' own experiments, 2,000 mg. of this compound per kg. per day in the diet for 23 days caused an increase of 2.9 days in the T_{50} ($p = 0.01$) as compared to untreated controls. One-quarter of this dose gave a 1.2 days' increase ($p = 0.05$) in the T_{50}[1] (13).

The fifth member of the group of sulfones mentioned above, Promizole, is quite different from the others in that it is a heterocyclic compound. That this compound possesses therapeutic activity comparable to DDS has been reported by Feldman and associates (14, 15).

[1] T_{50} = median survival time as determined by plotting cumulative percentage dead (on a probability scale) versus time in days on an arithmetic scale (13).

TABLE 1

Sulfones Showing No Significant Chemotherapeutic Activity in Experimental Tuberculosis in the Mouse

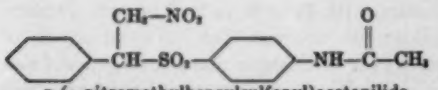
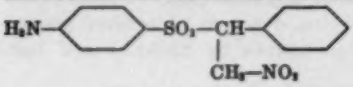
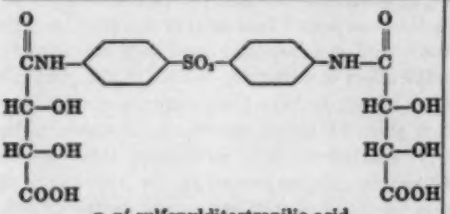
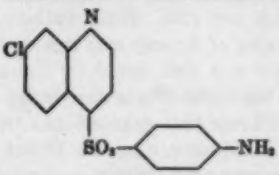
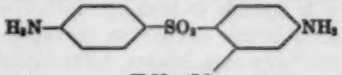
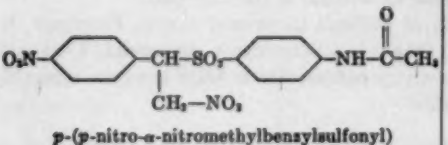
COMPOUND	MAXIMAL ACCEPTABLE DRUG INTAKE DAILY	DRUG INTAKE DAILY	INCREASE IN T_{50}	MIC FOR BCG*
	mg/kg	mg/kg	days	γ/ml
 p-(α-nitromethylbenzylsulfonyl)acetanilide	1,500	1,323	1.3	6.5
 p-(α-nitromethylbenzylsulfonyl)aniline	500	309	0.4	4.0
 p,p'-sulfonylditartranilic acid	1,000	1,092	0.5	>600
 7-chloro-4-sulfanilylquinoline	2,000	1,870	0.7	I†
 6-sulfanilylmetanilamide	500	524	2.2	600
 p-(p-nitro-α-nitromethylbenzylsulfonyl) acetanilide	2,000	2,208	0.2	90

TABLE 1—*Continued*

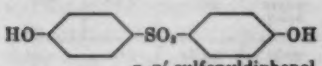
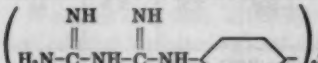
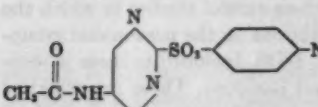
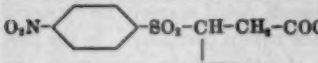
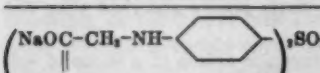
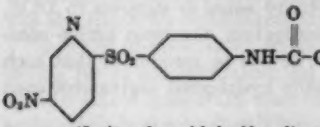
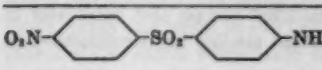
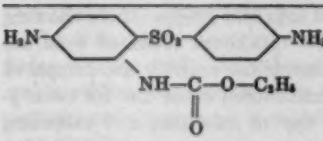
COMPOUND	MAXIMAL ACCEPTABLE DRUG INTAKE DAILY	DRUG INTAKE DAILY	INCREASE IN T_{50}	MIC FOR SCO*
	mg/kg	*mg/kg*	*days*	*γ/ml*
 *p,p'*-sulfonyldiphenol	>2,000	1,045	−1.5	20
 *p,p'*-sulfonylbis(1-phenylbiguanide),dihydrochloride	500 500	440 120	−3.5 −2.6	20 20
 *p*-(5-acetamido-2-pyrimidylsulfonyl)acetanilide	>2,000	1,782	1.0	100
 β-(*p*-nitrophenylsulfonyl)butyric acid	>2,000	918	−0.8	20
 N,N'-(*p,p'*-sulfonyldiphenyl)diglycine, disodium salt	2,000	1,815	−0.1	180
 *p*-(5-nitro-2-pyridylsulfonyl)acetanilide	250	250	1.4	1.5
 α-mercapto-*p*-(*p*-nitrophenylsulfonyl)acetanilide	500 500	386 113	−8.8‡ −0.5	5 5
 5-amino-2-sulfanilylcarbanilic acid, ethyl ester	250 250	247 85	−3.3‡ −0.8	60 60

TABLE 1—*Concluded*

COMPOUND	MAXIMAL ACCEPTABLE DRUG INTAKE DAILY	DRUG INTAKE DAILY	INCREASE IN T_{50}	MIC FOR BCG*
	mg/kg	*mg/kg*	*days*	*γ/ml*
	1,000	674	−5.8‡	15
	1,000	228	0.5	15
2-chloroethyl phenethyl sulfone				

* MIC for BCG = Minimal inhibiting concentration for BCG *in vitro*.
† I = Compound too insoluble to permit *in vitro* tests.
‡ = Compound apparently toxic at highest dose tested.

Recently, Titus and Bernstein (9) reported their careful studies in which the pharmacology of several sulfones having substitutions on the *para*-amino groupings were compared with the parent compound, DDS. Included in these investigations were Diasone, Promin, Sulphetrone, and Rodilone. These investigators obtained strong evidence to confirm the often voiced assumption that these compounds are hydrolyzed in the body, chiefly through acid hydrolysis in the stomach, to give free DDS. Hence, such compounds could scarcely be expected to show greater therapeutic activity than does the parent compound. In the case of Diasone, the hydrolysis led to the formation of intermediate substances, one of which appeared to be a reaction product of formaldehyde and DDS. It was found that all of the derivatives studied were more poorly absorbed than the parent compound.

Studies on the pharmacology and chemotherapeutic action of a series of sulfones have also recently been described by Smith, Jackson, and Bauer (16). Besides the well-known di-substituted compounds such as Promin and Diasone, a series of mono-substituted compounds were included. Several of these compounds were said to have chemotherapeutic activity equal or superior to DDS. According to the data presented by these investigators, the most active compound they tested was the *n*-propyl derivative. It will be recognized that such alkyl derivatives are more stable than the readily hydrolyzed derivatives such as Promin.

During the past few years a considerable number of sulfones have been studied in experimental tuberculosis in the standardized mouse test employed in this laboratory (17). The results of some of these studies are summarized in the present paper.

OBSERVATIONS

The compounds studied have been separated into two groups: those showing little, if any, chemotherapeutic activity at the maximum tolerated dose are listed in table 1; while those which showed significant activity are compared in table 2. In all cases the compounds were administered in the diet for twenty-three days, beginning two days prior to the day of infection, and extending through the twenty-first day thereafter.

Each of the compounds listed in table 2, at a proper level in the diet, was found capable of protecting mice infected with tuberculosis, to the extent that the T_{50} of treated mice was significantly greater than that of the corresponding untreated controls. The data presented in this table comprise averages of results obtained in the number of replicate tests indicated in the last column, Only with Promin and DDS were sufficient tests run to allow dosage-response curves to be drawn. These are shown in figure 1.

It can be seen that, if the log of the ratio of the T_{50} of treated to the T_{50} of control mice is plotted against the log of the daily dose, approximately a straight line is obtained. Since the ratio

$$\frac{\text{LOG } \frac{(T_{50} \text{ Treated})}{(T_{50} \text{ Controls})}}{\text{LOG } 10 \times \text{millimols/kg/day}}$$

appears to be essentially independent of the dose for a given compound, it may be used as a reasonable quantitative expression of antituberculous property in this test. It follows that the higher this ratio, the greater is the therapeutic response at a given dose and, therefore, the greater the therapeutic efficacy. The ratios obtained by this method of calculation for several of the more active sulfones studied are listed in table 3.

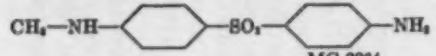
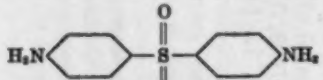
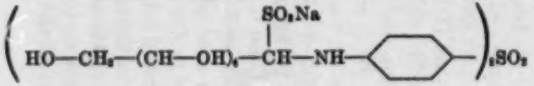
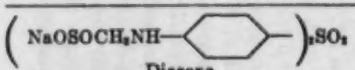
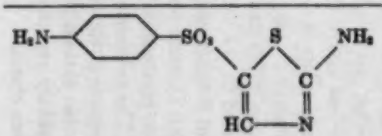
The data shown in table 3 have been examined statistically, and it was found that the compounds may be aligned in groups showing significantly different responses, at the 95 per cent confidence limits. Thus compound MC 2264 and DDS are approximately equal in activity, and are the most active of the group tested. Promin and Promizole are next in activity, and approximately equal to each other. Next come Diasone and Rodilone. The writers' experience with Sulphetrone has been very limited, but the indications are that this compound is very significantly less active than DDS or compound MC 2264. (Slight activity was also found for compounds MC 449 and MC 2283. See table 2.)

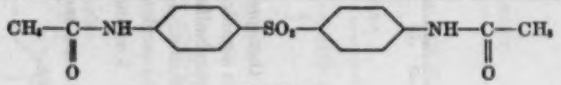
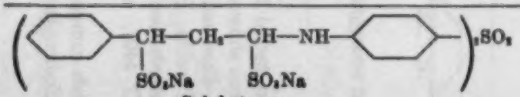
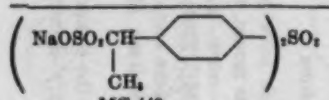
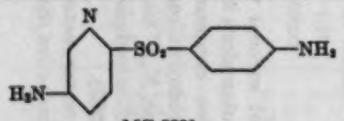
Since the di-substituted compounds listed above are hydrolyzed to DDS following *per os* administration (9), it may be asked why the various derivatives are less active than DDS itself on a molar basis. The most likely answer apparently exists in the work of Titus and Bernstein (9) who showed that following a single oral dose of 1.0 millimol per kg. of either DDS, Diasone, Promin, or Sulphetrone, DDS was found in the blood in all cases. The highest concentrations were found in the blood when DDS itself was administered, with Diasone, Promin, and Sulphetrone following in descending order. Interpretation of the findings with Diasone was complicated by the appearance of what appeared to be a reaction product of formaldehyde and DDS.

The compounds discussed in the previous paragraph are readily hydrolyzed because of the easily cleaved carbon-nitrogen linkage. In compounds with more stable carbon-nitrogen linkages such as in compound MC 2264, hydrolysis is unlikely and the manner in which the body treats this type of structure has not been clarified.

TABLE 2

Sulfones Showing Significant Chemotherapeutic Activity in Experimental Tuberculosis in the Mouse

COMPOUND	MAXIMAL ACCEPTABLE DRUG INTAKE DAILY	DRUG INTAKE DAILY	TREATED ANIMALS T_m	CONTROL ANIMALS T_m	INCREASE IN T_m[a]	NUMBER OF TESTS
	mg/kg	*mg/kg*	*days*	*days*	*days*	
 MC 2264	250	136	29.5	20.2	9.3[c]	2
		66.5	26.8	20.2	6.6[c]	2
 Diaminodiphenylsulfone	150	138	27.0	19.9	7.1[c]	2
		63.3	23.8	19.1	4.7[c]	4
		34.4	21.9	19.4	2.5[b]	6
 Promin	>2,000	2,131	30.9	20.3	10.6[c]	24
		1,037	28.6	19.9	8.7[c]	12
		527	23.0	18.6	4.4[c]	3
		257	27.1	22.3	4.8[c]	5
		128	21.2	20.4	0.8	4
 Diasone	2,000	1,118	25.9	19.5	6.4[c]	4
		462	21.7	18.8	2.9[b]	2
		260	23.9	20.0	3.9[c]	5
 Promizole	250	226	27.0	19.9	7.1[c]	2
		66	22.7	19.9	2.8[c]	2

 Rodilone	>2,000	2,234 1,129 549 254	27.0 26.0 24.3 24.0	20.2 19.2 20.2 19.2	6.8[c] 6.8[c] 4.1[c] 4.8[c]	1 1 1 1
 Sulphetrone	ca. 4,000	4,575 1,165	23.9 19.0	20.2 20.2	3.7[b] −0.8	1 1
 MC 449	500	242 61	24.0 21.1	19.8 19.8	4.2[c] 1.3	1 1
 MC 2283	1,000	1,010	21.5 20.5	18.8 18.8	2.7[b] 1.7	1 1

* As discussed in a previous publication (18), the Student's t test was used for comparing mean reciprocal survival times to determine the significance of differences between control and treated animals. Significant results above are marked with a, b, or c corresponding to significance of 5.0, 1.0, and 0.1 per cent.

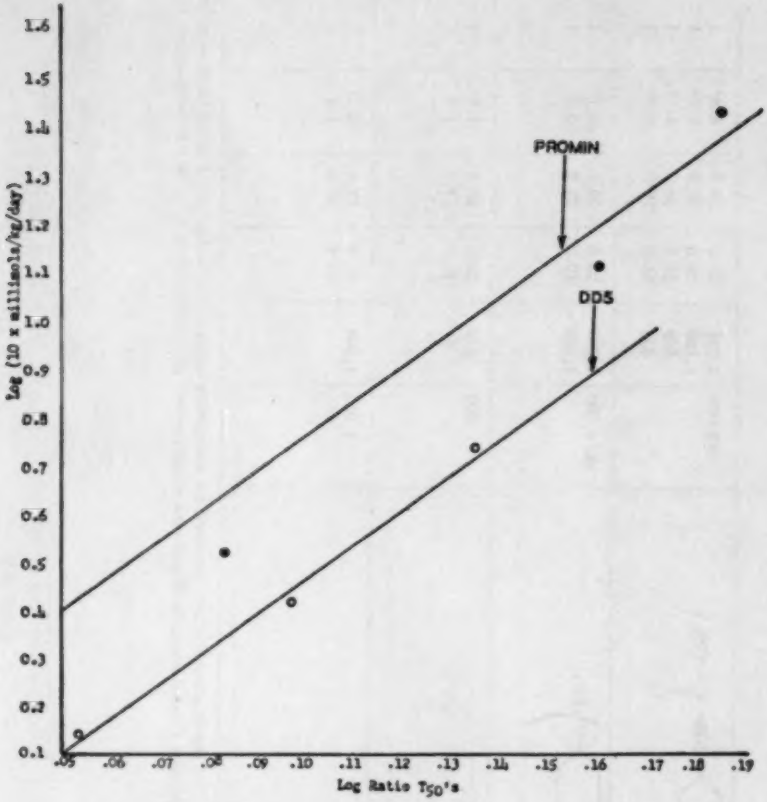


FIG. 1. Dosage response curves in experimental tuberculosis

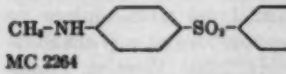
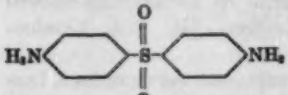
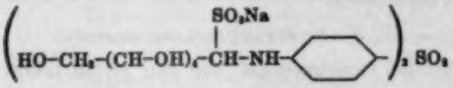
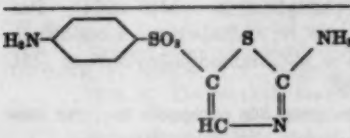
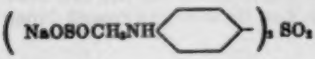
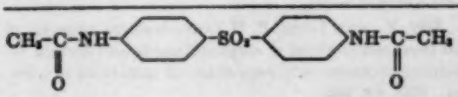
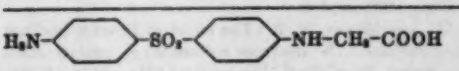
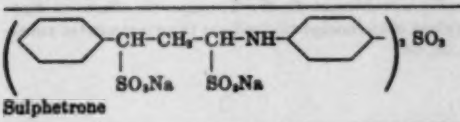
CONCLUSIONS

Of twenty-four different sulfones which have been tested for therapeutic activity in experimental tuberculosis in the mouse, fifteen showed no significant activity. The nine active compounds were: *p,p'*-diaminodiphenylsulfone, N-methyl-*p,p'*-diaminodiphenylsulfone (MC 2264), Promin, Promizole, Diasone, Rodilone, Sulphetrone, *N,N'*-bis(sodium acetaldehyde bisulfite) condensation product with *p,p'*-diaminodiphenylsulfone (MC 449), and 5-amino-2-sulfanilylpyridine (MC 2283).

In these studies in the mouse, none of the compounds compared on a molar basis was found to be more active than *p,p'*-diaminodiphenylsulfone.

TABLE 3

Relationship between Drug Dosage and T_{10} of Various Sulfones

DRUG	DAILY DOSE	RATIO OF T_{10}'s TREATED/CONTROLS	LOG RATIO OF T_{10}'s / LOG (10 × MILLIMOLS/KG/DAY)
	Millimols/kg/day		
 MC 2264	0.52	1.46	0.230
	0.25	1.33	0.312
			Average 0.271
 Diaminodiphenylsulfone	0.56	1.36	0.178
	0.26	1.25	0.233
	0.14	1.13	0.363
			Average 0.258
 Promin	2.7	1.52	0.127
	1.3	1.44	0.142
	0.68	1.24	0.112
	0.33	1.21	0.160
			Average 0.135
 Promizole	0.89	1.36	0.141
	0.26	1.12	0.118
			Average 0.130
 Diasone	2.6	1.33	0.0875
	1.0	1.15	0.0607
	0.6	1.20	0.1018
			Average 0.0833
 Rodilone	6.7	1.34	0.0697
	3.4	1.35	0.0851
	1.7	1.20	0.0644
	0.76	1.25	0.1098
			Average 0.0823
 Ciloprine	6.4	1.36	0.0739
	3.4	1.07	0.0192
	1.6	1.27	0.0861
			Average 0.0597
 Sulphetrone	5.1	1.18	0.0421
	1.3	1.04	0.0153
			Average 0.0287

CONCLUSIONS

Quimioterapia de la Tuberculosis. IV. Estudios con Sulfonas en el Ratón

De veinticuatro distintas sulfonas que fueron comprobadas con respecto a su actividad terapéutica en la tuberculosis experimental del ratón, quince no revelaron mayor actividad. Los otros nueve compuestos fueron: *p,p'*-diaminodifenilsulfona, N-metil-*p,p'*-diaminodifenilsulfona (MC 2264), Promina, Promizol, Diasona, Rodilona, sulfetrona, N,N'-bis(bisulfito de acetaldehido sódico) producto de condensación con *p,p'*-diaminodifenilsulfona (MC 2283), 5-amino-2-sulfanililpiridina (MC 2283).

En estos estudios en el ratón, ninguno de los compuestos comparados a base molar resultó ser más activo que la *p,p'*-diaminodifenilsulfona.

CONCLUSIONS

Chimiothérapie de la tuberculose. IV. Etudes des sulfones chez la souris

Su vingt-quatre sulfones qui ont été expérimentées pour leur action thérapeutique dans la tuberculose expérimentale de la souris, quinze n'ont pas donné la preuve d'une activité significative. Les neuf composés étaient: *p,p'*-diaminodiphénylsulfone, N-méthyl-*p,p'*-diaminodiphénylsulfone (MC 2264), Promine, Promizole, Diasone, Rodilone, sulphétrone, N,N'-bis(sodium acétaldéhyde bisulfite) produits de condensation avec la *p,p'*-diaminodiphénylsulfone (MC 2283), 5-amino-2-sulfanilylpyridine (MC 2283).

Dans ces études sur la souris, aucun des composés comparés sur une base molaire n'a été trouvé plus actif que le *p,p'*-diaminodiphénylsulfone.

Acknowledgment

The authors are indebted to Mr. K. A. Brownlee for the statistical analyses mentioned in the text, and to Dr. F. Y. Wiselogle and Mr. W. A. Lott for their kind counsel during the course of these studies.

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THE ENHANCEMENT OF GROWTH OF DIHYDROSTREPTOMYCIN-RESISTANT STRAINS OF TUBERCLE BACILLI BY DIHYDROSTREPTOMYCIN, A FUNCTION OF INITIAL pH VALUE OF THE MEDIUM[1,2]

CHARLES HURWITZ

(Received for publication January 15, 1951)

INTRODUCTION

The effect of the pH of the medium on the growth of tubercle bacilli and on streptomycin inhibition of the growth has been studied by many workers. Rich (21) cited Möllers (14) as reporting growth of tubercle bacilli in medium with a pH as low as 4. Dubos and Middlebrook (4) reported that growth occurred in their medium at pH 5.5 to 8.2. Initiation of growth was optimum at pH 6.4 to 6.7.

Loo and associates (12), in studying the assay of streptomycin by the paper-disc plate method found that the size of the zone of inhibition increased markedly with increasing pH. Abraham and Duthie (1) found that an increase in acidity of the medium decreased the antibacterial activity of streptomycin. Wolinsky and Steenken (26) found that the bacteriostatic effect of streptomycin diminished as the acidity of the culture medium increased from pH 7.7 to 5.2, the greatest decrease in streptomycin activity occurring between pH 6.6 and 5.9. Murray and Finland (15) also found a 20- to 80-fold reduction in activity of streptomycin at pH 5.8 as compared with the activity at pH 8.0. None of these investigators who studied the effects of pH on streptomycin activity worked with tubercle bacilli.

Hurwitz and Miller (8) found no apparent decrease in streptomycin activity at pH 6.0 for a sensitive strain of *M. tuberculosis*. A resistant strain of the same organism behaved like a "dependent" strain at pH 6.0 in that it grew well in high concentrations of streptomycin but grew poorly in the absence of the drug. Accordingly, the following investigation was undertaken in an attempt to study this phenomenon in detail.

METHODS

The cultures of *M. tuberculosis* which were studied were maintained in Dubos Tween 80-albumin liquid medium. Six- to eight-day-old cultures were adjusted to 70 per cent transmission at 520 mμ. with a Coleman Junior spectrophotometer, as described in a previous report (9). The inoculum consisted of 0.2 ml. (2×10^{-6} gm. dry weight) of this 70 per cent

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[1] From the Streptomycin Research Laboratory, Laboratory Service of Halloran VA Hospital, Staten Island, New York.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

suspension per 10.0 ml. of medium. A resistant strain of H37Rv, obtained from the Trudeau Laboratory, was used unless otherwise indicated.

A simpler medium[3] was used for the experimental studies. The Tween 80 was replaced by Triton A-20 except where noted, and albumin, glucose, and glycerin were omitted. Although this simple medium supported less growth than Tween 80-albumin medium, growth was adequate for the purposes of these experiments. It had the advantages of being easy to prepare and to adjust to the desired pH, and the Triton A-20 did not contain any oleic acid impurities which are found in Tween 80 (4).

The medium was prepared in ten-ninths concentration and tubed in 9.0 ml. quantities in Coleman 19 by 150 mm. O.D. tubes. After sterilization, 1.0 ml. streptomycin solution (as the dihydrostreptomycin sulfate salt) was added to give the desired concentration of streptomycin and medium. At each pH value, 6 dihydrostreptomycin concentrations (0, 1, 10, 100, 500, and 1,000 γ per ml.) were set up in duplicate. Per cent transmission readings were made at 520 mμ. and the dry weights of tubercle bacilli were calculated from a corrected curve by the method described in an earlier paper (9).

The pH values of the media were determined after sterilization and dilution with dihydrostreptomycin and are referred to as the initial pH. Dihydrostreptomycin sulfate has weakly acidic properties and had only a very slight effect on the pH of the medium. Even when dihydrostreptomycin was added to make a concentration of 1,000 γ per ml., the initial pH was never depressed more than 0.03 pH units.

RESULTS

The initial pH values for the first experiment were 5.60, 5.78, 5.95, 6.15, 6.35, and 6.55. The organism studied was a resistant strain of H37Rv.[4] The results of the experiment may be seen in figures 1 through 8.

At initial pH 6.55, only small differences, hardly visible to the naked eye, were found among all dihydrostreptomycin concentrations, although slightly greater growth occurred in higher dihydrostreptomycin concentrations than in the lower concentrations. At this initial pH 6.55, the strain behaved like a resistant tubercle bacillus.

At initial pH 6.35 and 6.15, the variations in growth between low and high concentrations of dihydrostreptomycin became slightly greater, since the amount and rate of growth at the three highest concentrations of the drug increased. At initial pH 5.95, the variations in growth became progressively greater, for the rate of growth in the 0, 1, and 10 γ per ml. streptomycin concentrations decreased markedly.

At initial pH 5.78, growth at 0, 1, and 10 γ per ml. streptomycin ceased, while growth in 100 and 500 γ per ml. concentrations decreased. At initial pH 5.60, growth occurred only in the 1,000 γ per ml. tubes.

In figure 7, the growth after fourteen days is plotted as a function of the initial pH of the medium. As may be seen, when the initial pH was lowered, the amount of dihydrostreptomycin necessary to produce maximum growth in this medium

[3] The medium consisted of KH_2PO_4, 1.0 gm.; Na_2HPO_4 (anhydrous), 2.5 gm.; sodium citrate, 1.5 gm.; $MgSO_4 \cdot 7H_2O$, 0.6 gm.; asparagine, 2.0 gm.; bactocasitone, 2.0 gm.; ferric ammonium citrate, 0.05 gm.; Triton A-20, 1.0 gm.; distilled water, 1,000 ml.

[4] Obtained through the courtesy of W. Steenken, Jr., The Trudeau Laboratory, Trudeau, New York.

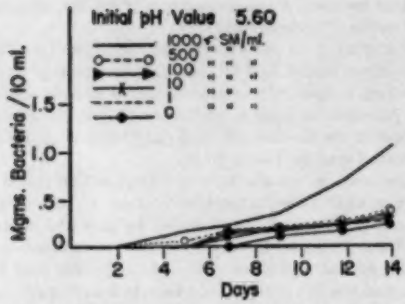

FIG. 1. The effect of initial pH and DHSM concentration on the growth of a DHSM-resistant strain of *M. tuberculosis* (H37Rv). Initial pH 5.60.

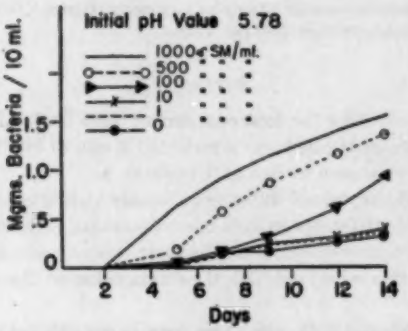

FIG. 2. The effect of initial pH and DHSM concentration on the growth of a DHSM-resistant strain of *M. tuberculosis* (H37Rv). Initial pH 5.78.

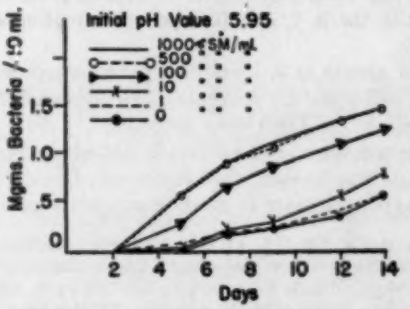

FIG. 3. The effect of initial pH and DHSM concentration on the growth of a DHSM-resistant strain of *M. tuberculosis* (H37Rv). Initial pH 5.95.

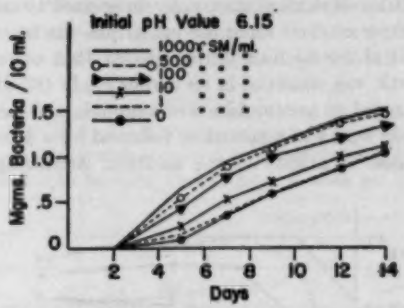

FIG. 4. The effect of initial pH and DHSM concentration on the growth of a DHSM-resistant strain of *M. tuberculosis* (H37Rv). Initial pH 6.15.

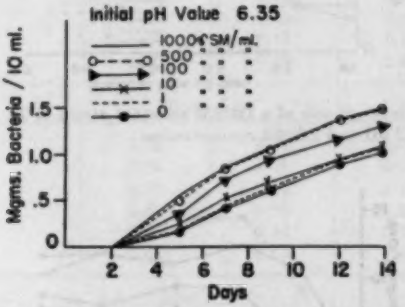

FIG. 5. The effect of initial pH and DHSM concentration on the growth of a DHSM-resistant strain of *M. tuberculosis* (H37Rv). Initial pH 6.35.

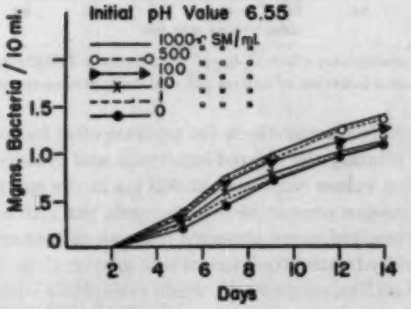

FIG. 6. The effect of initial pH and DHSM concentration on the growth of a DHSM-resistant strain of *M. tuberculosis* (H37Rv). Initial pH 6.55.

increased. At all pH levels studied streptomycin seemed to enhance growth, but the effect became more marked when the initial pH was below 6.15.

An increase in pH of the medium during growth that corresponded closely to the amount of growth was observed in an earlier study (8). Henley and Le Duc (7), among others, noted an accumulation of ammonia and increase of pH during the first two to three weeks of incubation, followed by a later disappearance of ammonia and increase of acidity of the medium. Accordingly, in the present

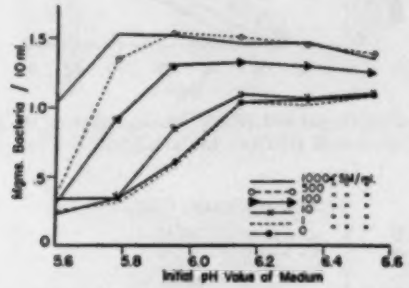

FIG. 7. Fourteen days' growth of a DHSM-resistant strain of *M. tuberculosis* (H37Rv) as a function of initial pH and DHSM concentration.

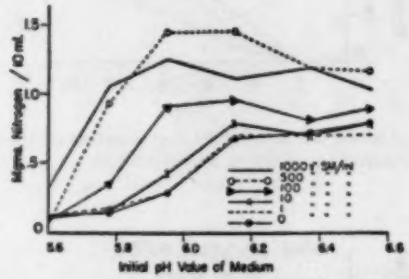

FIG. 8. Ammonia production after 14 days' growth by a DHSM-resistant strain of *M. tuberculosis* (H37Rv) as a function of initial pH and drug concentration.

study, the presence of free ammonia in the medium after fourteen days of growth was determined by diluting the cleared supernate and Nesslerizing the dilution. Per cent transmission values were read at 460 mμ in the spectrophotometer and the milligrams of nitrogen present as free ammonia per 10.0 ml. of medium were calculated from a standard curve prepared from an ammonium sulfate solution. Concentrations of dihydrostreptomycin sulfate greater than 100 γ per 13 ml. as the streptomycin base formed a cloudy, white precipitate with Nessler's reagent. The precipitate became increasingly heavy and voluminous and formed with greater rapidity as the concentration of the drug increased. At less than 100 γ

per 13 ml. of Nesslerized solution, there was no positive test for ammonia, nor was a precipitate formed during the time required for a transmission reading (ten minutes after the addition of the reagent). In the determinations reported

TABLE 1

Effect of Initial pH of Medium and Dihydrostreptomycin Concentration on Growth of Dihydrostreptomycin-Resistant Strains of Tubercle Bacilli

Milligrams Dry-Weight Bacteria after 14 Days' Growth per 10.0 Ml. Medium

DHSM CONCENTRATION	INITIAL pH OF MEDIUM			
	5.6	5.8	6.0	6.2
	Strain J 39			
γ/ml.				
0	0.10	0.15	0.26	0.56
1	0.05	0.00	0.19	0.59
10	0.10	0.05	0.15	1.06
100	0.05	0.05	0.43	1.23
500	0.05	0.15	1.28	1.26
1,000	0.05	0.61	1.40	1.40
	Strain J 40			
0	0.10	0.15	0.26	0.40
1	0.05	0.10	0.15	0.37
10	0.05	0.10	0.10	0.50
100	0.00	0.05	0.33	1.18
500	0.05	0.10	1.40	1.42
1,000	0.05	0.40	1.48	1.52
	Strain I 63			
0	0.10	0.10	0.15	0.43
1	0.10	0.10	0.10	0.46
10	0.05	0.05	0.15	0.61
100	0.00	0.00	0.30	0.75
500	0.00	0.10	0.82	0.96
1,000	0.00	0.23	0.88	1.02
	Strain F 44			
0	0.30	0.33	0.63	1.48
1	0.19	0.26	0.67	1.48
10	0.19	0.26	1.02	1.46
100	0.19	0.26	1.52	1.53
500	0.10	1.48	1.64	1.62
1,000	0.19	1.66	1.60	1.60

in this experiment, the concentration of streptomycin base never exceeded this value and was usually well below it.

The results are presented in figure 8. As may be seen by comparison of figures

7 and 8, a close agreement between growth and ammonia production was found, with two notable exceptions. Less ammonia was found at initial pH levels 5.60 and 5.78 than would be expected from the amount of growth; more ammonia was found, especially in the 500 γ of dihydrostreptomycin concentrations, at initial pH values 5.95 and 6.15. This disparity may be an indication of a pH optimum for a deaminase or deamidase enzyme.

TABLE 2

Effect of Initial pH of Medium and Dihydrostreptomycin Concentration on Growth of a Dihydrostreptomycin-Resistant Strain of H37Rv

Tween 80 Used as Detergent

Milligrams Dry-Weight Bacteria after 14 Days' Growth per 10.0 Ml. Medium*

DHSM concentration	Initial pH of medium					
	5.51	5.69	5.83	6.05	6.25	6.48
γ/ml.						
0	1.06 + .04	1.22 + .15	1.97 + .01	1.98 + .0	2.07 + .03	2.14 + .10
1	1.07 + .02	1.43 + .09	1.83 + .05	1.98 + .06	2.01 + .17	2.02 + .05
10	1.14 + .04	1.55 + .05	1.95 + .0	2.26 + .04	2.24 + .06	2.14 + .04
50	1.57 + .05	1.72 + .0	2.32 + .14	2.66 + .16	2.45 + .0	2.58 + .04
100	1.78 + .06	1.94 + .16	2.76 + .14	2.77 + .05	2.88 + .02	2.96 + .24

* Average of duplicate values

TABLE 3

Effect of Initial pH of Medium and Dihydrostreptomycin Concentration on Growth of a Dihydrostreptomycin-Resistant Strain of H37Rv

No Detergent Used in the Medium

DHSM concentration	Initial pH of medium					
	5.45	5.61	5.81	6.02	6.23	6.43
γ/ml.						
0	1	4	8	8	8	8
1	1	4	8	8	8	8
10	1	6	8	8	8	8
100	5	7	8	8	7	8
500	7	8	7	7	7	7
1,000	7	8	7	7	6	6

The numbers indicate an arbitrary standard for measurement of the relative amounts of growth after 14 days. Number 1 indicates just visible growth; number 8 indicates heavy submerged growth and surface completely covered with a thin pellicle.

The effect of the initial pH of the medium on growth of a resistant strain in the presence of dihydrostreptomycin has been repeated with a number of other resistant strains recently isolated from tuberculous patients. All resistant strains of *M. tuberculosis* thus far studied have shown the same effect. The results of the study of 4 such resistant strains may be seen in table 1.

A study to determine whether the detergent used affected the results was then undertaken. In the first experiment, 0.05 per cent of Tween 80 was substituted for the Triton A-20. Although the amount of growth obtained was greatly increased, probably because of oleic acid stimulation (5), the effect of the initial pH on the growth of a resistant strain in the presence of dihydrostreptomycin was again demonstrated (table 2). At all initial pH levels studied, increases in dihydrostreptomycin concentration increased growth of the resistant strain, but the per cent stimulation of growth decreased as the initial pH was raised.

In another experiment, no detergent was added to the medium. As a result, growth was not dispersed and could not be read in a spectrophotometer. An arbitrary visual scale was used to obtain the results found in table 3. The stimulation of growth by dihydrostreptomycin at low initial pH levels occurred despite the absence of the detergent.

DISCUSSION

As was pointed out in an earlier paper (8), the stimulating effect of dihydrostreptomycin on growth of resistant strains of tubercle bacilli at pH values of approximately 6 might conceivably be of significance when the drug is administered to patients with tuberculosis. Caseous material, pus, and inflamed tissue have been shown to develop local acid reactions (see literature reviews by Dubos (3) and Staines and Cárdenas (24)). It is possible that continued use of streptomycin therapy after the emergence of drug-resistant microorganisms may favor the growth of the tubercle bacilli *in vivo*.

In connection with this observation, it is interesting to note that Steenken, Oatway, and Petroff (25) and Smithburn (22) have induced a marked loss of virulence in tubercle bacilli by growing them on acid media with pH 6.0 to 6.1. It remains for further work to clarify the role of the acid reactions of infected tissue.

Strains which grow in the presence of streptomycin, but not in the absence of the drug, are called "dependent." Such strains of bacteria have been reported by several workers (10, 11, 13, 18, 19, 23, 27, 28). The relationships between sensitive, resistant, and dependent variants are puzzling. Paine and Finland (18) reported that dependent variants were isolated only from sensitive populations of *Staph. aureus*, *E. coli*, *Ps. aeroginosa*, and *P. morganii*, and reversion of dependent strains resulted only in sensitive strains. Yegian, Budd, and Vanderlinde (28), on the other hand, found a high incidence of streptomycin-resistant variants in dependent populations of tubercle bacilli. Yegian and Vanderlinde (29) isolated a streptomycin-dependent variant of *Mycobacterium ranae* from a resistant population. They were unable to isolate a dependent variant from a sensitive population of this organism. Murray, Wilcox, and Finland (16) reported some reversions of streptomycin-resistant gram-negative bacilli to a sensitive status after repeated subculturing in the absence of the antibiotic. In the present study, streptomycin-resistant strains of tubercle bacilli showed a definite tendency toward streptomycin dependence when the initial pH of the medium was

lowered. Further work is planned to study the effect of initial pH on the sensitivity to streptomycin of dependent and partially resistant strains.

The pH effect on streptomycin activity reported in this paper differs from the effect of pH on streptomycin activity previously reported, since all previous work has apparently been done with sensitive strains. In general, previous work has shown that streptomycin activity increased with pH and that a sharp fall in activity was shown below 6.6. The results reported here show that initiation of growth of resistant strains was favored by high concentrations of dihydrostreptomycin below pH 6.5 and that increasing the concentrations of streptomycin decreased growth lag. As the initial pH was lowered below pH 6, more dihydrostreptomycin was required to promote growth.

These effects cannot be attributed to effects on the drug because the dihydrostreptomycin did not become less active as pH decreased, but actually stimulated growth. Streptomycin solutions have been shown to have great stability between pH 3 and 7 (17, 20).

An explanation of the effect of initial pH on the streptomycin reaction with resistant strains of tubercle bacilli cannot be attempted with our present state of knowledge. Other workers have reported pH effects on metabolism of tubercle bacilli. Block, Matter, and Suter (2), and Geronimus (6) reported that the stimulation of respiration by lactic, butyric, and acetic acids, as well as by long chain fatty acids, was increased by lowering the pH. Dubos (3) found that aliphatic acids inhibited growth of tubercle bacilli in low concentrations and that the inhibitory activity of the acids increased as pH decreased.

SUMMARY

As the initial pH of the medium was decreased below 6.5, dihydrostreptomycin stimulated the growth of drug-resistant strains of tubercle bacilli. The lower the initial pH, the greater was the amount of dihydrostreptomycin necessary for stimulation. At initial pH of approximately 6, the resistant strains did not grow in the absence or in low concentrations of dihydrostreptomycin, but grew well in high concentrations of the drug.

SUMARIO

La Aceleración del Desarrollo de Cepas Resistentes de Bacilos Tuberculosos por la Estreptomicina, Función del Valor pH Inicial del Medio

A medida que se rebajaba a menos de 6.5 el tenor inicial del pH del medio, la dihidroestreptomicina excitaba el desarrollo de cepas resistentes de bacilos tuberculosos. Mientras más bajo el pH inicial, mayor era la cantidad de dihidroestreptomicina necessaria para tal excitación. A tenores iniciales aproximadamente de 6 de pH, no se desarrollaban cepas resistentes a falta o con bajas concentraciones de estreptomicina, pero sí se desarrollaban bien en altas concentraciones de dihidroestreptomicina.

RESUME

(L'accélération du développement de souches résistantes de bacilles tuberculeux causée par la streptomycine, fonction de la valeur initiale du pH du milieu)

Quand le pH initial du milieu était amené au dessous de 6,5, la dihydrostreptomycine stimulait la croissance de souches résistantes du bacille tuberculeux. Plus le pH initial était bas, plus il fallait de dihydrostreptomycine pour obtenir cette stimulation. Avec un pH initial d'environ 6, les souches résistantes ne se développaient pas en l'absence de dihydrostreptomycine ou lorsque sa concentration était basse; mais leur développement se faisait bien lorsque la concentration de l'antibiotique était élevée.

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Case Reports

SURGICAL MANAGEMENT OF GIANT AIR CYSTS OF THE LUNGS[1,2]

Physiologic Improvement after Resection

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INTRODUCTION

Large pulmonary cysts may impair function to such a degree that patients with this condition appear dyspneic on exertion or may even become "respiratory cripples" at rest. Resection of these cysts may result in definite postoperative mitigation of the labored breathing (9).

Reference in the literature to the pathologic physiology of pulmonary air cysts is scant. Kaltrieder and Fray (4) reported detailed studies of the pulmonary function of six patients with pulmonary cysts and emphysematous bullae. Postoperative studies were not available in any of their patients. Recently Baldwin and her associates (2) published their thorough observations on the physiologic patterns of pulmonary function in sixteen patients with large pulmonary air cysts, blebs, or bullae. Four of these patients were restudied following surgical resection of their lesions.

The present report describes two patients with giant pulmonary cysts. Clinical dyspnea experienced by each of these patients was relieved by resection of the cysts. Pulmonary function studies done before, during, and after bilateral cystectomy on one of these patients are reported.

Comparison of Congenital Bronchogenic Cysts and Acquired Cysts

Single large cysts in an otherwise normal lung parenchyma have not posed any great therapeutic problem subsequent to the development of safe methods of open-chest anesthesia and intrathoracic surgical dissection. The majority of these single cysts appear to be of congenital origin. They may cause symptoms due to pressure upon the air passages, the esophagus, and upon large vessels. They are subject to overdistention, infection, or hemorrhage. If it is necessary, these single cysts can be removed readily, although the operation may be complicated by the presence of infection.

The therapeutic problem is decidedly more complicated in the case of acquired pulmonary cysts of large size. These are frequently multiple and bilateral, and may be associated with irreversible fibrotic and emphysematous changes within the lung parenchyma. This pathologic process has been called variously *giant emphysema*, *bullous emphysema*, *acquired cysts*, and *pneumatocele*. The victims of this disease process are likely to be in middle life or older. They may present a clear-cut history of antecedent acute respiratory disease as a precursor to increasing shortness of breath. Sputum is scant, mucoid, and nonpurulent. Because these cysts are frequently bilateral and because the

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[2] Presented at a meeting of the Society of Clinical Surgery in New Haven, Connecticut, on November 10, 1950.

parenchyma may be extensively involved, this group of cases has been considered by most physicians to be beyond the help of resectional therapy. Marked initial impairment of pulmonary function and the advanced age of some of these patients have likewise served as deterrents to surgical treatment.

Treatment

Various surgical trials for all types of cysts have been recorded in the past, and the techniques have varied from simple aspiration (1) or tube drainage (5, 7, 11) to partial lung resection or radical excision of lobes (6, 8, 9).

Not infrequently, attempted simple aspiration of these cysts has been carried out in the physician's office, sometimes because of a mistaken diagnosis of interpleural air. When tension has existed in the cystic areas, transient relief may have been obtained by this procedure (1), but the temporary benefit is far outshadowed by the dangers of resultant bleeding, superimposed pneumothorax, pleural fistula, and infection. Any one of these complications is likely to be poorly tolerated by a patient with impaired pulmonary function. Cauterization of fistulous bronchial openings in the cyst walls has been practiced. Thoracotomy with suture of bronchial openings (13), excision and plication of the parenchymatous wall (7), and catheter drainage of the cysts have been tried (15). For localized lesions, total or segmental lobectomy (6) and even pneumonectomy (8, 9) have been carried out.

Careful study of roentgenograms in cases of acquired cystic disease may reveal patterns of collapsed parenchyma due to pressure by the overdistended cysts. These atelectatic areas may be more clearly demonstrated by overpenetration techniques and particularly by laminagraphy. In this way a more optimistic opinion can be obtained of the functional improvement to be anticipated after resection. A favorable physiologic trend is to be expected following resection of large cysts in patients with a recent history of progressive dyspnea, especially when this is accompanied by progressively unfavorable roentgenographic changes. Moreover, the possibility of obtaining physiologic improvement is better in relatively young patients and in the patients without evidence of cardiac disease.

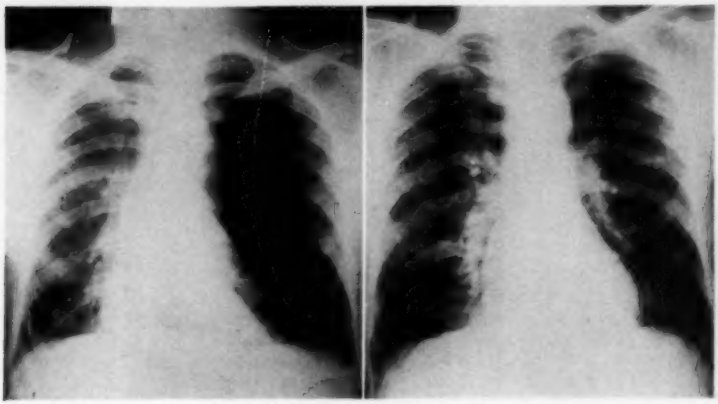
Prior to operation an evaluation of pulmonary function should be undertaken. The purpose of this is: (*1*) to judge the urgency and the probable risk of operation; and (*2*) to provide a baseline by which postoperative improvement can be estimated. For patients with lesser degrees of dyspnea and without cyanosis, careful fluoroscopy, together with determination of the maximum breathing capacity, the resting and the walking ventilation (12), will be sufficient. If the patient is uncomfortably short of breath, however, or if cyanosis is present, it is advisable to seek evidence of anoxia by studying the oxygen saturation and the carbon dioxide content of the arterial blood and to test for emphysema by determination of the volume of residual air. Differential bronchospirometry is desirable, but is not essential. It may be tolerated poorly by an extremely dyspneic patient.

Since it is usual that function is improved after the removal of the cyst, conservative resections may be carried out even in the face of initial, very poor pulmonary function if the proper supportive measures are maintained during operation and afterwards until improvement is effected.

The two cases presented illustrate the substantial improvement in pulmonary function which may occur following thoracotomy with cystectomy for cystic disease. The first patient had localized unilateral disease, but nevertheless was incapacitated by dyspnea. The second patient had extreme bilateral involvement, and at the time of the first of his two operations was a respiratory "cripple" of the severest degree. Results of serial tests of the pulmonary function of the second patient are presented in detail.

CASE REPORTS

Case 1. The patient was a farmer who was 58 years old at the time of operation. In the summer of 1946 he first noticed dyspnea on exertion but was able to continue his work. In March 1947, after running up stairs, he experienced dull pain in his left anterior chest and increasing shortness of breath. Roentgenograms of his chest were obtained and were said to show "a collapse of the lung." He was admitted to New Haven Hospital in September 1947. At that time roentgenograms of the chest showed a large, apparently solitary, pulmonary cyst occupying almost the entire left hemithorax, with slight, induced basilar pneumothorax (figure 1). Well-defined lung markings on the left were visible only



Case 1

FIG. 1. (Left) Before operation. A giant air cyst displaces almost all of the parenchyma of the left lung. Compressed lung tissue is visible adjacent to the left cardiac border. The mediastinum is pushed to the right, and the right lung is partially compressed. A small pneumothorax pocket is present at the base laterally.

FIG. 2. (Right) Nine months after cystectomy of the dorsal segment of the left lower lobe. The left lung has expanded completely.

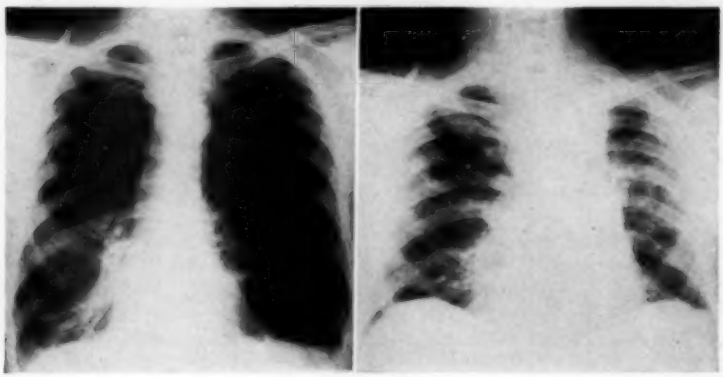
in a medial triangular area at the extreme base. The heart and mediastinum were shifted to the right with depression of the right hemidiaphragm, and there was partial compression of the right lung.

Operation: Under endotracheal general anesthesia, a left anterior intercostal incision was made with transection of the fourth costal cartilage. A large pulmonary cyst was found attached to and replacing the apical segment of the left *lower* lobe. This cyst was dissected free, together with a small amount of surrounding compressed lung tissue. The lung was sutured and the pleura repaired with fine silk. The chest was closed without drainage. Postoperative course was uneventful.

The patient was last seen in June 1949 at which time he was well, free from chest pain and shortness of breath, and was working on his farm. A chest roentgenogram at that time showed good expansion of the left lung with some residual fibrous strands and evidence of mild bilateral emphysema (figure 2). The mediastinal structures were in the midline.

Case 2. The patient was a shipping clerk who was 45 years old at the time of operation. He felt well until March 1938 when he had sudden onset of fever to 102°F., cough, shortness of breath, and some cyanosis. The diagnosis of pneumonia of the left lung was made by his family physician, and he was treated at home. A few weeks later he was able to return to work and during the following summer was able to fish and swim and carry on all of his usual activities without troublesome dyspnea.

In November 1938, he became aware of gradually increasing shortness of breath on exertion and of occasional wheezing in the chest. He was seen as an outpatient at the Laurel Heights Sanatorium where the first roentgenogram of his chest was taken. This film showed no visible parenchyma on the left, while at the same time similar but more limited changes in the upper half of the right lung were noted (figure 3).



Case 2

FIG. 3. (Left) Before surgery. Bilateral giant air cysts displace all of the parenchyma of the left lung and the upper half of the right lung.

FIG. 4. (Right) Two and one-half years after completion of surgery. Giant cysts have been resected from left upper lobe, apex of left lower lobe and right upper lobe.

Over the next nine years the patient was followed as an outpatient. During this period he continued to work. Serial roentgenograms showed no change. Gradually, however, he noticed increased shortness of breath which at the end of this period was present on the slightest exertion. This course was reflected in serial studies of his pulmonary physiology which were begun in 1942.

In July 1947, his family physician attempted left thoracentesis in an effort to relieve dyspnea. This resulted in left pneumothorax and increased discomfort. He entered New Haven Hospital for study in September 1947. At that time he had slight cyanosis of his lips and nail beds. An attempt at differential bronchospirometry was abandoned when the patient had a pontocaine reaction.

Operation: In November 1947, a cystectomy was performed at New Haven Hospital under intratracheal gas-oxygen-ether anesthesia. A huge cyst was removed from the left upper lobe and a smaller cyst along with the mediastinal border of the apical segment were also resected. Several small cysts of the lower lobe were seen at operation but were not removed. Postoperative course was uneventful. Clinical and physiologic improvement were marked. Serial roentgenograms of the chest demonstrated expansion of the left lung, with some residual fibrosis on that side, and shift of the mediastinum to the left.

Over the next four months the patient was seen as an outpatient at New Haven Hospital. By January 1948, he was feeling much better and could walk a mile on the level and climb stairs without shortness of breath for the first time in nine years. This clinical improvement was paralleled by favorable change in his pulmonary physiology.

The patient re-entered New Haven Hospital in April 1948. At this time one large cyst was removed from the right upper lobe. Additional cysts seen in the region of the right hilus and the pectoral segment of the same lobe were not resected. No gross cyst could be visualized in the right middle and lower lobes at the time of operation. Again his postoperative recovery was uneventful.

TABLE 1

Values of Pulmonary Function in Case No. 8

	BEFORE SURGERY	FOUR MONTHS AFTER CYSTECTOMY, LEFT LUNG	TWENTY-NINE MONTHS AFTER CYSTECTOMY, RIGHT LUNG	NORMAL OR PREDICTED VALUES FOR THIS PATIENT
I. Body surface area (in square meters)	1.71	1.82	1.91	1.81
II. Lung volumes:				
Vital capacity (in cc.)	1,038	2,350	3,130	3,820
Residual air (in per cent of total lung volume)	—	—	32	23
III. A. Maximum breathing capacity (in L/min)	28	74	97	117
B. Ventilation (in L/min/m^2 of B.S.A.)				
Basal	5.3	4.4	3.7	3.1
Walking	6.4	8.8	8.3	9.0
IV. Arterial blood:				
Oxygen saturation (in per cent)				
Basal	88.5	—	88.5	>92.0
After exercise	93.1	—	94.5	>94.0
Carbon dioxide content (in volume per cent)				
Basal	48.4	—	—	52.0
After exercise	43.8	—	—	47.8
V. Dyspnea:				
At rest	+	0	0	0
Walking on level	++	0	0	0
Climbing stairs	+++	0	0	0

After May 1948 the patient was entirely free from symptoms. He returned to work and has noticed no fatigue or shortness of breath in performing any of his activities. Serial roentgenograms showed complete expansion of the right lung with relatively little fibrosis on this side and no pleural thickening (figure 4). Once again, clinical improvement was paralleled by definite improvement in his pulmonary physiology.

STUDIES OF PULMONARY PHYSIOLOGY

The serial studies of pulmonary physiology on the second patient performed before, during, and after bilateral cystectomy gave perceptible evidence of the improvement in pulmonary function which can result after operation (table 1). With giant, bilateral cysts, the patient's maximum ventilation was as low as 28 liters per minute before operation

(predicted value for this patient 117 liters). His breathing reserve at that time was so poor that he became short of breath when carrying out simple daily activities and was comfortable only at rest. His vital capacity was reduced to 1,038 cc. (predicted value 3,820 cc.). At the time of the left cystectomy, this marked impairment of ventilation had resulted in slight arterial anoxia at rest. The immediate effect of exercise was to raise the oxygen saturation of the arterial blood to just below the normal value. The carbon dioxide content of the arterial blood before and after exercise was normal.

Following resection of the huge cyst from the left lung, there was prompt improvement of ventilation in two weeks. Four months after operation the maximum breathing capacity had risen to 74 liters and the vital capacity to 2,350 cc., more than double the preoperative levels. These favorable changes occurred as the parenchyma of the left lung expanded, in spite of the fact that there was roentgenographic evidence of fibrosis in this expanded lung. It is possible that the shift of the mediastinum to the left side actually improved the ventilation of the parenchyma compressed at the right base and that this, in turn, contributed to the increase in the total ventilation observed after the first operation. Serial differential bronchospirometric studies were not available to support this theory.

After the second operation when the giant cyst was removed from the right lung, there was again an immediate favorable response of ventilation followed by further gradual improvement over the next one and one-half years. At the end of that time the patient's maximum breathing capacity was 83 per cent of the estimated normal for his age and surface area. On the basis of fluoroscopy and the appearance of the lung fields in the final roentgenograms, it was concluded that the right lung was contributing the major portion of the total ventilation. After bilateral cystectomy, the volume of residual air was 32 per cent of the patient's total lung volume. This is somewhat more than the predicted value of 23 per cent, but values less than 35 per cent indicate absence of significant emphysema. It was of interest that, although there was such marked improvement in ventilation, slight arterial anoxia persisted after bilateral cystectomy. There was no symptomatic manifestation of this physiologic abnormality.

DISCUSSION

Single or multiple air-containing pulmonary cysts, if they do not cause symptoms, frequently do not require surgery. The patient should be followed clinically and by serial roentgenograms during his lifetime to detect any unfavorable developments that would require surgical intervention. Three major complications may occur: (*1*) the cysts may become infected; (*2*) a bronchopleural fistula may develop; and (*3*) the cysts may, by compressing the adjacent pulmonary parenchyma, produce shortness of breath. If the onset of one or more of these complications is acute, it may be necessary to resort to prompt surgery. On the other hand, if the cysts produce gradual appearance of dyspnea and this symptom has not yet become too severe, it is then possible to observe the patient for weeks or years before deciding if and when surgery should be done. Cystectomy appears to be the treatment most likely to bring about lasting cure and prompt control of infection, bronchopleural fistula, hemorrhage, or dyspnea.

There is a natural tendency to regard severe shortness of breath as a contraindication to resection of pulmonary cysts; whereas actually this symptom may be an urgent indication for cystectomy. A giant cyst or cysts may so markedly compress adjacent good lung parenchyma that the patient's breathing reserve is reduced to the point of severe dyspnea. Fortunately, in many of these patients, removal of the ballooned cyst, or cysts, allows the collapsed parenchyma to expand promptly and the dyspnea will be relieved to the degree that the ventilation is improved. It is necessary, of course, to determine by tests

of pulmonary function before operation that the dyspnea is primarily the result of collapse of parenchyma by the cysts and is not produced by some other mechanism such as heart failure, extensive parenchymal infiltration, fibrosis, or marked diffuse emphysema.

Baldwin, Cournand, and Richards (2) believe that surgery is mandatory where dyspnea is troublesome, provided there is no anoxia or significant diffuse emphysema. They warn that patients with ventilatory insufficiency accompanied by pronounced anoxia and emphysema are poor surgical risks.

SUMMARY

Two cases are presented in summary to illustrate the therapeutic advantage of limited resection (cystectomy) for alleviation of dyspnea due to the presence of giant air cysts of the lungs. Both patients were operated upon more than three years ago.

Serial studies of pulmonary function, made before and after surgery are reported for one patient in whom bilateral cystectomy was performed.

SUMARIO

Asistencia Quirúrgica de los Quistes Aéreos Gigantes de los Pulmones

Los dos casos sumarizados demuestran la ventaja terapéutica que entraña la resección limitada (quistectomía) para el alivio de la disnea debida a la presencia de quistes aéreos gigantes en los pulmones. Ambos pacientes fueron operados hace más de tres años.

Para un caso en que se ejecutó una quistectomía bilateral, se presentan estudios seriados de la función pulmonar, realizados antes y después de la operación.

RÉSUMÉ

Traitement chirurgical des kystes aériens géants du poumon

Deux cas ont été présentés sommairement pour illustrer l'avantage thérapeutique offert par la résection limitée (cystectomie) pour soulager la dyspnée causée par la présence de kystes aériens dans le poumon. Ces deux malades avaient été opérés plus de trois ans auparavant. Des études en série de la fonction pulmonaire effectuées avant et après l'intervention ont été décrites. Il s'agissait d'un cas ayant subi une cystectomie bilatérale.

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SPONTANEOUS PNEUMOTHORAX, THE RESULT OF A RUPTURED DIAPHRAGM COMPLICATING PNEUMOPERITONEUM[1]

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The increased use of pneumoperitoneum within recent years as either a principal form of therapy in tuberculosis or as an adjunct to other recognized forms of treatment has resulted in a general knowledge of the complications which may arise during the maintenance of this type of collapse therapy. Recently a case of fatal tension pneumothorax secondary to a ruptured diaphragm in a patient receiving pneumoperitoneum has been reported (1). Since that publication, a second similar but nonfatal instance of this complication has been observed by the authors.

CASE REPORT

J. P., a 22-year-old white male, World War II veteran, was admitted to Homer Folks Tuberculosis Hospital on December 27, 1949 because of unstable pulmonary tuberculosis. He had a pneumonic onset of his disease in September 1948 while serving with the armed forces in Germany. He received penicillin and streptomycin, the latter drug in a total dosage of 37.5 gm. between October 27 and November 29, 1948. In December he was transferred to the Fitzsimons Army Hospital, Denver, Colorado, where pneumoperitoneum was induced on December 29, 1948 and supplemented by phrenic nerve crushing in February 1949. Following his transfer to a Veterans Administration hospital in the East, the pneumoperitoneum was continued uneventfully with weekly refills of air averaging 700 to 800 cc., until his departure from that hospital against medical advice in August 1949. Thereafter he received similar refills weekly in the outpatient department of Homer Folks Hospital until December 27, 1949 when he was admitted as a patient because of the presence of tubercle bacilli in the sputum, evidence of instability of his tuberculosis by chest roentgenogram, and increase in symptoms which included a productive cough, anorexia, fatigue, and right-sided pleurisy.

On physical examination the patient looked well nourished and developed, and he appeared neither acutely nor chronically ill. Impaired resonance and diminished breath sounds without rales were noted over the right lung to the second rib anteriorly and fourth vertebral spine posteriorly, and the left lung was clear to percussion and auscultation. Examinations of blood and urinalyses were within normal limits. A complement fixation test for syphilis was positive with a titer of 3. Sputum remained persistently positive for tubercle bacilli on concentration. A chest roentgenogram on admission (figure 1) revealed a moderate amount of apparently fibrotic infiltration above the second anterior rib and fifth vertebral spine on the right enclosing several rather poorly defined, small, radiolucent areas suggesting cavity formation. A very large pneumoperitoneum space was noted, with the dome of the diaphragm extending up to the level of the fourth rib anteriorly on the right and the fifth on the left. By fluoroscopic examination the right hemidiaphragm had resumed function as manifested by a negative "sniff test" and absence of paradoxical motion.

On a regimen of bed rest modified only by full bathroom privileges and pneumoperitoneum, little change was noted clinically after seven weeks. Refills averaged 800 to 850 cc. weekly with initial pressures averaging +7, +9; and final pressures +10, +12 cm. of water. A chest roentgenogram obtained on February 23, 1950 (figure 2) revealed a moderate-sized ring shadow 4.5 by 3 cm. of uncertain significance at the right base, which was pre-

[1] From the Homer Folks Tuberculosis Hospital, Oneonta, New York.

sumed to represent a large emphysematous bleb. Assuming that pneumoperitoneum and right phrenic nerve crushing were not going to be effective in bringing about cavity closure, it was decided, following fluoroscopy and his last refill on February 27, to abandon the pneumoperitoneum and consider right thoracoplasty or right upper lobectomy. Meanwhile, it was contemplated that, when the pneumoperitoneum was approximately half absorbed, streptomycin and para-aminosalicylic acid therapy should be administered so as to facilitate better cavity drainage. Endobronchial tuberculosis involving the bronchus draining the right upper lobe cavity was suspected, but bronchoscopy was not done to confirm this. The patient was fluoroscoped on March 10, 1950, at which time no change was observed in the pneumoperitoneum.

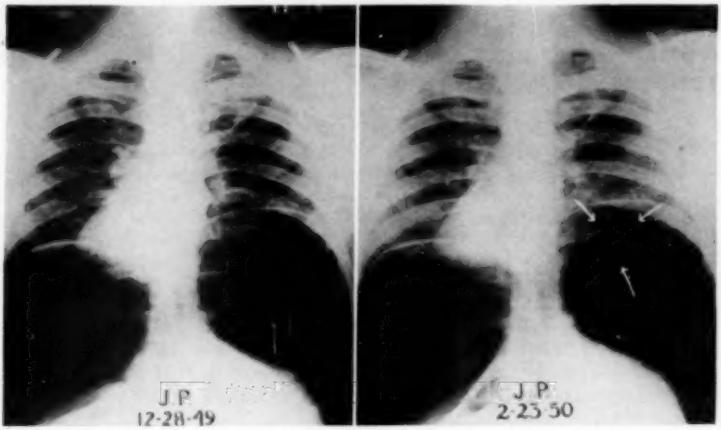

FIG. 1. (Left) Roentgenogram showing extent of disease and pneumoperitoneum at the time of admission, December 28, 1949.

FIG. 2. (Right) Roentgenogram showing appearance of bleblike shadow on the pleural surface of the diaphragm on the right, as outlined by arrows.

While at home on leave of absence from the hospital on the night of March 11, 1950, his sleep was disturbed by vague pains in the right side of his chest anteriorly and slight dyspnea. At 2:30 a.m. the following morning, upon sitting up in bed, he experienced sudden severe pain in the same region of his chest. The pain radiated upward into his neck and shoulder on the same side, and was accompanied by marked dyspnea and a sensation of heavy pressure in both ears. On his return to the hospital by taxi at 7:30 a.m., dyspnea and chest pain ontinued unabated and there were signs of moderate shock. Fluoroscopic examination revealed the appearance of a large pneumothorax on the right, with moderate reduction in size of the existing pneumoperitoneum. The findings suggested the presence of a rent in the diaphragm through which air had escaped upward from the peritoneal cavity into the right pleural space. Following the demonstration of intrapleural pressure readings of +14, +9 cm. of water, 2,250 cc. of air were aspirated, with reduction in manometric readings to −9, −1, with marked relief of symptoms, although by fluoroscopic examination a moderate amount of air was still seen both in the peritoneal and right pleural cavities. There was no recurrence of dyspnea or chest pain. A chest roentgenogram obtained on March 15, 1950 (figure 3) revealed apparently complete disappearance of the penumoperitoneum, but the right lung remained approximately 60 per cent collapsed by pneumothorax. Significantly, the moderate-sized ring shadow which was present at the right base on the roentgenogram of February 23, 1950 was not now visible. Thoracoscopy was per-

formed on March 17, 1950 in order to observe the pleural surface of the right hemidiaphragm, and was followed by insertion of an indwelling catheter and application of continuous suction until the lung was completely re-expanded. At the time of thoracoscopy a small slit measuring 1 cm. in length was observed in the posterolateral aspect of the right hemidiaphragm as well as a pedunculated cystlike mass measuring 2 cm. in diameter on the posterior portion of the diaphragm from which a biopsy was obtained. Subsequent histologic examination revealed the tissue to be connective tissue and muscle fibers compatible with normal diaphragmatic tissue. A roentgenogram obtained on March 18 (figure 4) prior to the removal of the suction drainage tube showed the right lung to be completely re-expanded with no air either in the pleural or peritoneal cavities. A right upper-stage thoracoplasty

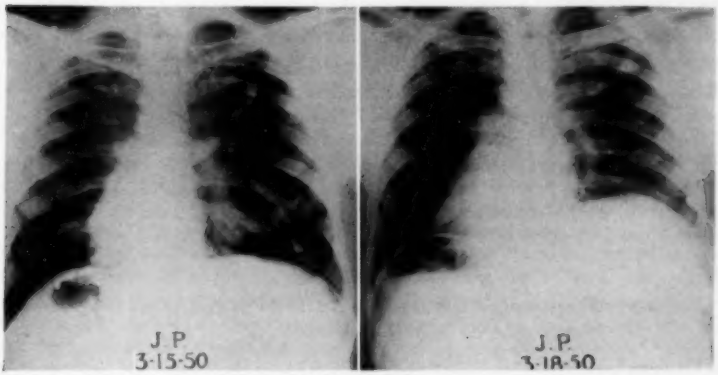

FIG. 3. (Left) Roentgenogram showing spontaneous pneumothorax and disappearance of pneumoperitoneum.

FIG. 4. (Right) Roentgenogram showing complete re-expansion of right lung and absence of pneumoperitoneum.

was subsequently performed on April 4, 1950 followed on April 26 by a right upper lobectomy and block resection of a disease-bearing portion of the superior segment of the lower lobe. Following these procedures the patient had an uneventful convalescence.

COMMENT

This case is similar to that previously reported by Yannitelli and associates (1) in at least three respects. First, the spontaneous pneumothorax did not occur immediately following a pneumoperitoneum refill in either instance; the intervals being thirteen days in the present case and nine days in the previously reported cases. The reason for the delayed rupture may be, as suggested by the writers of the previous paper, that the differential pressure between the intraperitoneal and intrapleural pressure is greatest sometime after a pneumoperitoneal refill, thus facilitating rupture at this time.

Second, in the previously reported case the spontaneous pneumothorax occurred following a period of unusual activity. In the present case the episode occurred while the patient was on a leave of absence prior to surgery, a period during which his activities may be assumed to have been much greater than during his previous period of therapy in the hospital. In this respect, it might be advisable to caution patients who are receiving pneumoperitoneum, particularly on an ambulatory basis, to abstain so far as possible from activities tending to increase intraperitoneal pressure.

Third, in each instance the diaphragmatic rupture was preceded by roentgenographic changes indicative of blebs produced on the pleural surface of the diaphragm by the stretched muscle fibers prior to their rupture. Although the frequency of such blebs in tuberculous patients receiving pneumoperitoneum is unknown, the presence of similar shadows in roentgenograms of patients receiving pneumoperitoneum should serve in the future as a warning that diaphragmatic rupture may be imminent.

Diagnosis in this case was confirmed by the thoracoscopic examination which revealed the presence of a slitlike aperture in the diaphragm. In addition, an intact cystlike structure was encountered which had the histologic appearance of diaphragmatic tissue. It is assumed that it was the rupture of a similar structure which produced the initial spontaneous pneumothorax.

SUMMARY

A nonfatal spontaneous pneumothorax which resulted from a ruptured diaphragm in a patient receiving pneumoperitoneum is reported. The rupture was preceded by the appearance of a cystlike structure as noted by roentgenographic examination. The diagnosis was confirmed by thoracoscopy with demonstration of a rupture 1 cm. in length in the posterolateral aspect of the right hemidiaphragm. The possibility of the occurrence of this complication in patients receiving pneumoperitoneum, particularly on an ambulatory basis, must be considered. Prompt evacuation of the air from the pleural cavity resulted in the prevention of a fatal tension pneumothorax in the case presented.

SUMARIO

Neumotórax Espontáneo, Resultado de una Rotura del Diafragma que Complicó un Neumoperitoneo

Preséntase un caso de neumotórax espontáneo no letal debido a ruptura del diafragma en un enfermo que recibía el neumoperitoneo. La ruptura fue precedida de la aparición de una formación quistoidea según registró el roentgenograma. El diagnóstico lo confirmó la toracoscopia al descubrir una rotura de 1 cm. de largo en la cara postero-lateral del hemidiafragma derecho. En los enfermos tratados con neumoperitoneo, en particular en forma ambulante, hay que considerar la posible ocurrencia de esta complicación. La rápida evacuación del aire de la cavidad pleural logró impedir la producción de un neumotórax inflado letal en el caso descrito.

RESUME

Pneumothorax spontané résultant d'une rupture diaphragmatique consécutive à un pneumopéritoine

Présentation d'une observation de pneumothorax spontané, non fatal, par rupture du diaphragme consécutive à un pneumopéritoine. La rupture avait été précédée par l'apparition d'une image kystique observée sur les radiogrammes. Le diagnostic fut confirmé par la thoracoscopie qui montrait une rupture d'un centimètre de longueur dans le segment postérolatéral de l'hémidiaphragme droit. La possibilité de cette complication chez des malades traités par le pneumopéritoine doit être prise en considération, en particulier dans les cas ambulatoires. L'évacuation rapide de l'air de la cavité pleurale a évité excès de pression du pneumothorax qui aurait pu être fatal dans le cas présenté.

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MEDIASTINAL EMPHYSEMA COMPLICATING INDUCTION OF PNEUMOPERITONEUM[1, 2]

MAURICE J. SMALL AND R. E. FREMONT

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Although there are a number of reports of mediastinal emphysema associated with spontaneous pneumothorax or occurring as a complication of pneumothorax (1–10), only three reports (11, 12, 13) were found of mediastinal emphysema as a complication of therapeutic pneumoperitoneum. Jehn and Nissen (11) state without other details that mediastinal emphysema was once observed after a pneumoperitoneum. Banyai and Jurgens (12) report seven such cases and document their reports with roentgenographic demonstration of the mediastinal emphysema. However, Banyai states (12) "... while this complication (i.e., mediastinal emphysema) was not observed in patients whom we were treating by the subumbilical route, it was relatively frequent when air was injected by the subphrenic route." He further postulates that air reaches the mediastinum when the subdiaphragmatic approach is used "through the peripheral portion of the diaphragm that might have been traumatized by the needle ... the air elevates the basal parietal pleura, and dissecting it from the upper surface of the diaphragm reaches the mediastinum," so that these cases actually are not a complication of a true, localized pneumoperitoneum. Banyai subsequently reported (14) that only one of these seven cases of mediastinal emphysema occurred when the customary method of administering pneumoperitoneum by injecting the air abdominally in the region of the umbilicus was used. The other six cases all occurred following subdiaphragmatic administration of air. Simmonds (13) reported four cases of mediastinal emphysema in 12,500 pneumoperitoneum refills. The presence of the complication was diagnosed on the basis of clinical signs without roentgenographic confirmation.

None of the above mentioned reports of mediastinal emphysema complicating pneumoperitoneum (11–13) includes mention of the characteristic precordial crunch synchronous with systole described in the classical paper of Hamman (15). Simmonds (13) did note in one case "a superficial crepitant murmur synchronous with the heart beat." The present writers believe that the presence of mediastinal emphysema complicating pneumoperitoneum is probably often overlooked as a result of the practice of attributing the pneumoperitoneum patient's complaints of substernal discomfort, dyspnea, choking, neck pressure, dysphagia, and so forth to phrenic nerve irritation. Moreover, the procedures of auscultation for the Hamman sign or looking for roentgenographic evidence of mediastinal emphysema are not routinely employed. In the following case report, the diagnosis of mediastinal emphysema was confirmed by these findings, and, in addition, a phonocardiographic record of the systolic crunch was made.

CASE REPORT

F. M., a 28-year-old white male, was known to have had pulmonary tuberculosis since March 1947. A pneumothorax was induced on the right side at another institution in April 1947.

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[1] From the Chest Section and Cardiovascular Section, Medical Service, Halloran VA Hospital, Staten Island, New York.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

The collapse therapy was thought to be controlling his disease effectively until September 1949, when on routine roentgenographic examination a massive fresh lesion in the left upper lobe was noted. The patient was admitted to this hospital in October 1949, and therapy with streptomycin and PAS was begun after a preliminary trial of bed rest showed no significant regression of the lesion.

A pneumoperitoneum was induced May 1, 1950 in order to give the patient possible further collapse therapy. Two hundred and fifty cubic centimeters of air were injected by the subumbilical approach, which the patient tolerated without unusual complaints. A small pneumoperitoneum space was noted fluoroscopically following this induction. On the following day, May 2, 1950, a refill of 300 cc. was given by the same approach and the pneumoperitoneum space was noted fluoroscopically to be of greater size. One hour after this refill, while lying in bed, the patient began to complain of a pain in his throat. He also stated that

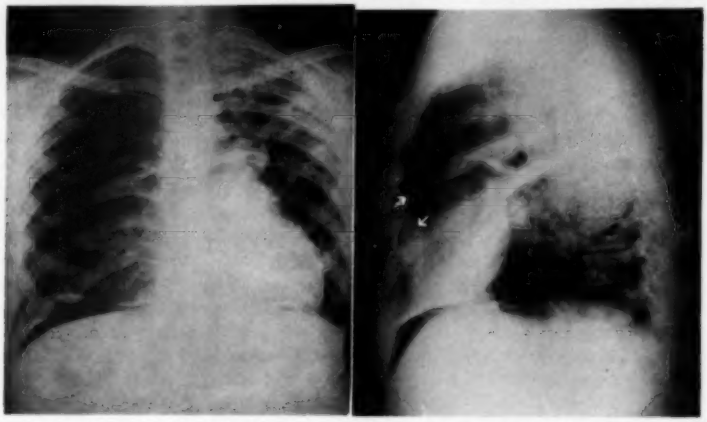

FIG. 1. (Left) May 3, 1950. Pneumomediastinum is demonstrated along the left superior mediastinal border by the arrows as a thin line outlined by air adjacent to the upper cardiac contour. A small pneumoperitoneum space is present.

FIG. 2. (Right) May 3, 1950. Left lateral view. The pneumomediastinum is seen as a thin line separated from the sternum by an air column.

he could not swallow food and had slight substernal discomfort. The patient looked well and was not dyspneic. Examination of the throat revealed no abnormality. There was no subcutaneous emphysema in the neck, suprasternal notch, chest wall, or abdomen. Auscultation over the cardiac apex revealed a loud systolic crunch; this was heard only with the stethoscope on the chest and was not audible to the unaided ear or to the patient, as occurred in some of Hamman's (15) cases. Blood pressure was 120 systolic and 80 diastolic in mm. of mercury; an electrocardiogram revealed no abnormality during or after this episode. On fluoroscopic examination, with the patient in left lateral position a small air space in the anterior chest was visualized with difficulty. The diagnosis of mediastinal emphysema was confirmed by antero-posterior and lateral roentgenograms (figures 1 and 2) on May 3, 1950. Phonocardiographic tracings were also recorded during the acute episode and after its clinical and roentgenographic disappearance (figure 3). The phonocardiogram during the acute episode resembles that described by Hoffmann, Pobers, and Merliss (16) and by Fagin and Schwab (17) in spontaneous mediastinal emphysema.

The patient's symptoms gradually subsided without treatment, and on May 4, 1950 only a small amount of air was noted subdiaphragmatically. Another attempt at pneumoper-

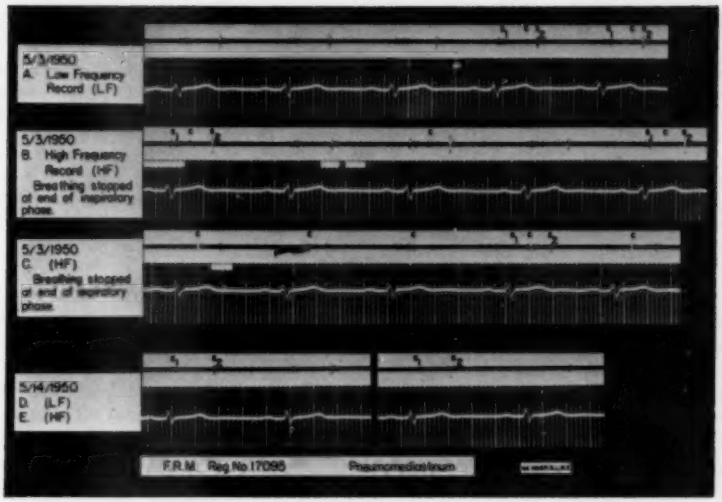

FIG. 3. Phonocardiographic tracings recorded during the acute episode and after its clinical and roentgenographic disappearance.

S_1—first sound; S_2—second sound; C—systolic crunch

A. Low frequency tracing obtained at left parasternal region, fourth intercostal space, reveals a small group of vibrations (C) present in late systole, of short duration and showing phasic changes in frequency and amplitude.

B and C. High frequency tracings show this group of vibrations to be of very high frequency, and of maximal intensity at the end of the expiratory phase.

D and E. These tracings obtained eleven days later are entirely normal.

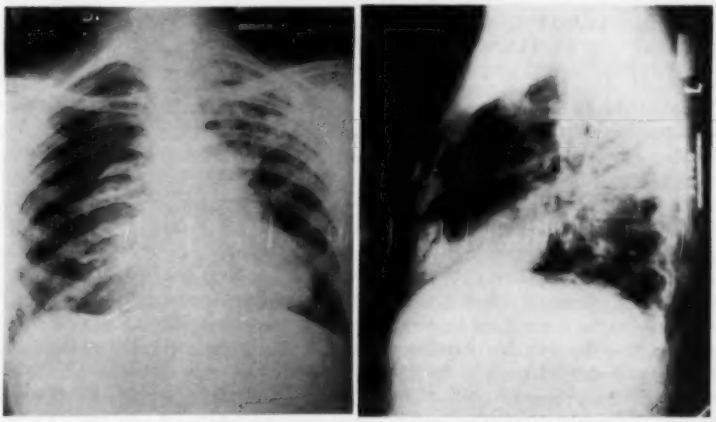

FIG. 4. (Left) May 23, 1950. The pneumomediastinum and pneumoperitoneum shown in figure 1 have now completely disappeared.

FIG. 5 (Right) May 17, 1950. Left lateral view compared to figure 2 now shows disappearance of the pneumomediastinum and pneumoperitoneum.

itoneum was made that day, for Banyai reported (14) that in one of his cases he continued pneumoperitoneum for eight months more without recurrence of the mediastinal emphysema. Hayes (18) states, however, that "mediastinal emphysema which results from a congenital defect in the attachments of the diaphragm can be relieved only by cessation of the pneumoperitoneum." In the present case, 200 cc. of air were cautiously given with recurrence of all symptoms two hours later. Within the next four days all symptoms as well as the systolic crunch disappeared; this was confirmed by subsequent roentgenograms (figures 4 and 5) and phonocardiogram (figures 3 D and E).

COMMENT

In the five cases reported by Banyai (12) and Simmonds (13), it was believed that air had ascended into the mediastinal space from the pneumoperitoneum space "through a hiatus of the diaphragm beside the esophagus or aorta" (13). With the large number of pneumoperitoneum refills given since this mode of therapy has enjoyed a rebirth of popularity, it is difficult to understand why mediastinal emphysema should not occur more often if this be the avenue of air travel. Hamman (15) states that air may reach the mediastinum from the retroperitoneal space; he does not mention the peritoneal space. Jehn and Nissen (11) experimentally injected air directly into the mediastinum of rabbits and dogs. Air was found along the esophagus and aorta, penetrating the diaphragm and collecting in the perirenal tissues. Joannides (19) demonstrated experimentally in the dog that:

> ...the air bubbles in the mediastinum extend upward toward the cervical fascia and downward through the post-esophageal areolar tissue to the mesentery and retroperitoneal tissues. At the hiatus esophagus of the diaphragm an anatomic study revealed the presence of a small inverted triangle, the sides of which were joined together by means of thin fibrous tissue. Under increased pressure from above, the air finds its way through the opening into the abdominal retroperitoneal tissues and spreads along the root of the mesentery downward to the fascia of the iliopsoas muscle and out through the inguinal ring to the superficial tissues in the abdominal wall. At the region of the perirenal areolar tissues frequently a bulla will form which in turn ruptures and allows the air to escape into the free peritoneal cavity thus causing a pneumoperitoneum.

Macklin (20) likewise demonstrated that air under pressure in the mediastinum descends into the retroperitoneal space.

In view of these experimental data the present writers believe that the pathogenesis is most likely as described by Joannides (19) and Macklin (20) but in the reverse order. That is to say, pneumoperitoneum under pressure ruptures through a weak portion of the peritoneum into the retroperitoneal space and thence proceeds along the large vessels to the esophageal and aortic foramina into the mediastinum. Direct ascent via a congenital defect in the attachments of the diaphragm has been hitherto assumed (12, 13, 18) but no experimental demonstration of this route has been reported. Moreover, the writers believe, in view of the renewed interest in pneumoperitoneum as a therapeutic procedure, that the diagnosis of mediastinal emphysema as a complication of this therapy will be more frequently made in the future. This will be the case particularly if the possibility of the occurrence of mediastinal emphysema in patients with vague complaints following pneumoperitoneum is kept in mind; if auscultation for the Hamman sign is performed; and if roentgenograms in antero-posterior and lateral projections are obtained. In the last named connection, it would seem that in questionable cases the maneuver utilized by Littmann (10) of taking the lateral roentgenograms with the patient in the

supine recumbent position, thus accentuating the air shadow anteriorly, should be particularly helpful in diagnosis.

SUMMARY

A case of mediastinal emphysema occurring as a complication of pneumoperitoneum induction, and confirmed by roentgenography and phonocardiography, is reported, and the probable pathogenesis is discussed.

SUMARIO

Enfisema Mediastínico como Complicación de la Inducción del Neumoperitoneo

El caso comunicado es de enfisema del mediastino, sobrevenido como complicación de la inducción de un neumoperitoneo, y confirmado por la radiografía y la fonocardiografía. En lo que se sepa, esta comunicación es la cuarta de su género.

RESUME

Emphysème médiastinal comme complication d'un pneumopéritoine

Un cas d'emphysème médiastinal survenu à la suite d'un pneumopéritoine, confirmé par la radiographie et la phonocardiographie, est rapporté. Selon les auteurs, ce cas est le quatrième faisant l'objet d'un rapport.

Acknowledgment

The writers wish to express their thanks for the cooperation of Dr. John A. Insolera who was the ward physician in charge of this patient.

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CARDIOSPASM SIMULATING MEDIASTINAL TUMORS[1,2]

HERBERT M. PERR

(Received for publication December 18, 1950)

Although many aspects of cardiospasm have frequently been described, the majority of case reports have emphasized the gastrointestinal symptoms, with only passing mention of respiratory and mediastinal disturbances. The case recorded below indicates the difficulties that may be encountered in arriving at the correct diagnosis.

CASE REPORT

The patient, a 28-year-old white male factory worker, was referred to the hospital on May 13, 1949 because of a persistent cough and the intermittent production of a copious, clear, watery sputum. Twelve years previous to his admission, he had had his first attack of an upper respiratory infection which was followed by a chronic cough persisting more or less to the time of admission. He was inducted into the Army in 1941 and served for four years, during which time he had several episodes of inadequately documented "pneumonias" which responded rapidly to sulfonamide therapy. Following separation from service, he received a disability pension for "chronic bronchitis."

In June 1948, the patient was re-examined for persistent cough and although his bronchial tree was revealed to be normal following a bronchogram, a suspicious radiopaque shadow was observed. Six months later (May 1949) he was admitted to this Veterans Administration hospital.

A system review was noncontributory except for the patient's comment that he suffered rapid weight losses during bouts of his upper respiratory infection, followed by rapid recovery. Frequently, following prolonged and intense coughing spells, he would regurgitate some food and liquid.

Physical examination revealed an alert, cooperative, somewhat apprehensive white male with no fever, cyanosis, dyspnea, or clubbing of the fingers or toes. Breath sounds were loud over the whole chest, and no rales were heard. No widening of the mediastinal dullness was perceived. Laboratory examination on admission showed a total erythrocyte count of 5,100,000 per cu. mm.; 15.7 gm. of hemoglobin; a total leukocyte count of 5,600 per cu. mm., with 54 per cent polymorphonuclear leukocytes, 37 per cent lymphocytes, 8 per cent monocytes, and 1 per cent eosinophils; and an erythrocyte sedimentation rate of 5 mm. per hour (Westergren). The sputum was scanty, watery, and contained a few gram-positive organisms, presumably *Streptococci*.

On the basis of the initial history and physical examination, a tentative diagnosis of chronic bronchitis and bronchiectasis was made. The first chest film obtained the day after admission completely modified this opinion and prompted a revision of the diagnostic investigation. The initial roentgenograms may be seen in figures 1a and 1b and revealed a normal pulmonary parenchyma and cardiovascular structures. A large ovoid density was present in the right paratracheal region and extended between the second and sixth thoracic vertebrae. At the level of the tenth thoracic vertebra on the right and the eleventh on the left, suggestive evidence of two soft tissue paravertebral masses was present. The ob-

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[1] From the Medical Service of the Bronx Veterans Administration Hospital, Bronx, New York.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

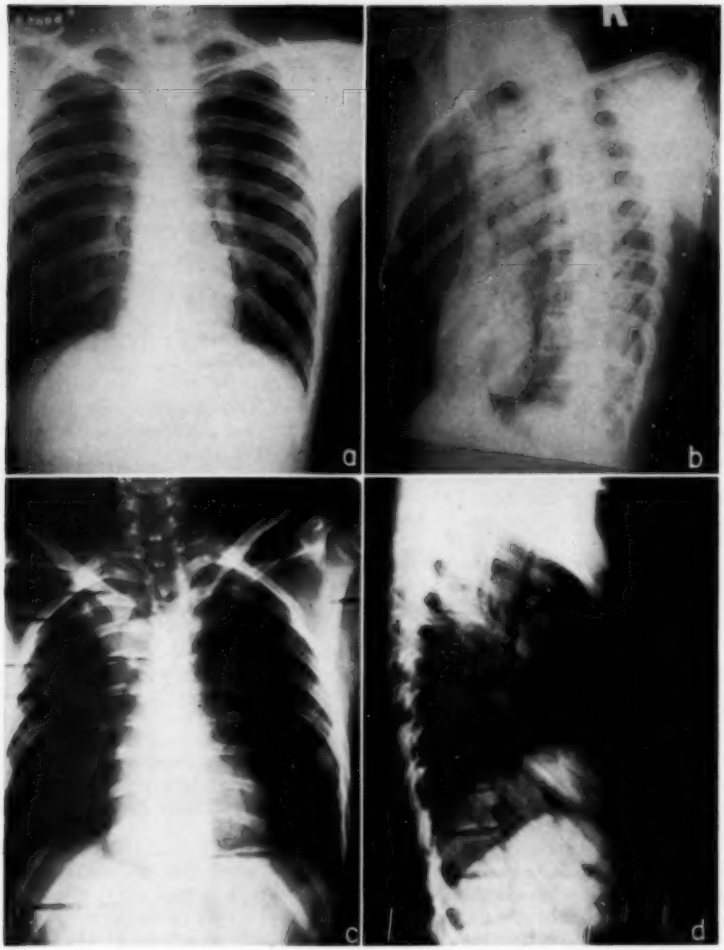

FIG. 1a. Postero-anterior roentgenogram of the chest taken May 13, 1949, the day of admission.

b. Left anterior oblique on May 16, 1949, indicative of the position of the lower mass.

c and d. Postero-anterior and right lateral exposures reveal no osseous disease, taken on May 16, 1949.

lique view demonstrated the presence of a rounded density behind the heart. These films were consistent with a diagnosis of lymphoma or Pott's abscess. Overexposed films of the chest taken several days later (figures 1c and 1d) failed to reveal any osseous, articular, or vertebral body abnormalities.

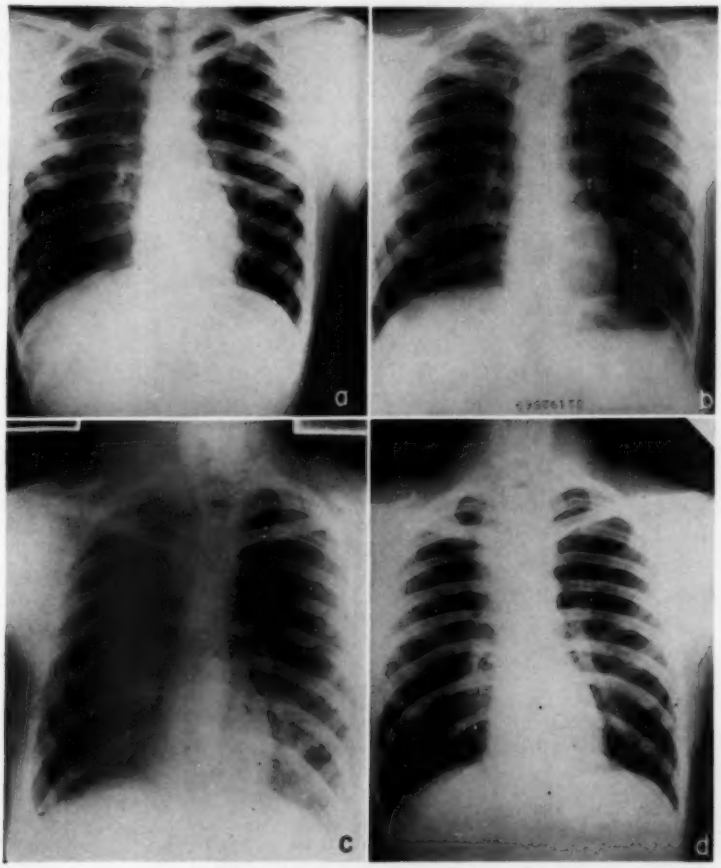

FIG. 2a. Postero-anterior roentgenogram of the chest taken in October 1937, after the first episode of pneumonia.

b. Postero-anterior roentgenogram of the chest, December 1941, when patient was inducted into the Army, revealing no obvious mediastinal pathology.

c. Postero-anterior roentgenogram, December 1945, at time of discharge from the Army, when the right paratracheal mass was now evident.

d. Postero-anterior roentgenogram of the chest, June 1948, revealing the static nature of the lesion.

Further laboratory tests were performed. The patient's second-strength PPD tuberculin test was strongly positive. The concentrations of the plasma proteins were within normal limits. Microscopic examination of a concentrated sputum smear revealed no acid-fast bacilli.

Soon after admission it was possible to obtain chest films which dated from the onset of his illness. Figure 2a shows the chest as it appeared in 1937 during the first attack of upper respiratory infection. No masses were evident then. The patient's Army induction film taken in 1941 (figure 2b) similarly revealed no masses. The roentgenogram (figure 2c) obtained at the time of discharge in 1945 demonstrates clearly the existence of the right paratracheal mass. In retrospect there is also a suggestion of the paravertebral mass at the eleventh thoracic vertebra. Figure 2d, taken four years later, demonstrates the static nature of the mediastinal mass. The bronchogram seen in figure 3 revealed no evidence of bronchial disease.

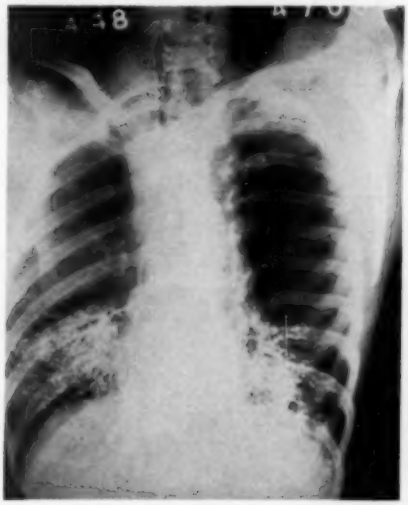

FIG. 3. Representative film of a bronchogram taken in September 1948 showing no bronchial disease.

While it was considered unlikely that a lymphoma would grow so slowly over a period of at least four and one-half years, this was considered to be the most likely possibility, and further attempts to corroborate the diagnosis were made. An esophagram and gastrointestinal series were performed with unexpected results. Figure 4a shows the barium mixture in a dilated and tortuous esophagus. The masses that had been considered to represent lymph nodes are clearly delimited as portions of the diseased esophagus. The dilatation may be seen in figure 4b, and the tortuosity in the right anterior oblique position in figure 4c. The smooth, conical termination typical of cardiospasm is shown in figure 4d.

Once the diagnosis was evident, the patient was interrogated anew. With prodding and the use of leading questions, he recalled a symptom that had been present for the past ten years. Frequently, after swallowing solid food, he would experience a sticking sensation in his mid-epigastrium which would disappear on hyperextension of his spine or following imbibition of a liquid. He now remembered that his cough was most often nocturnal in time.

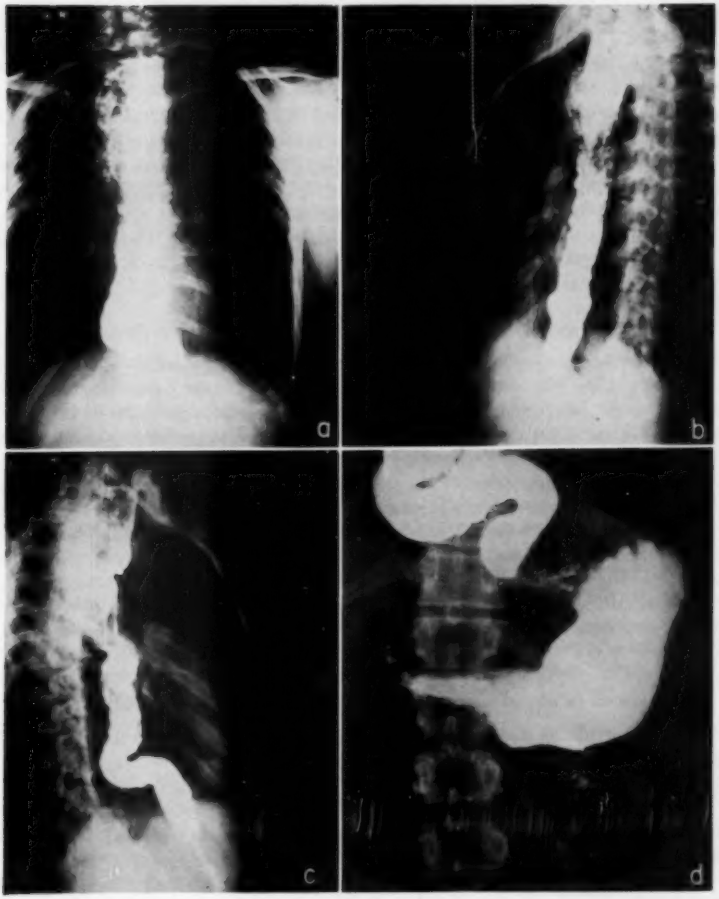

FIG. 4a. Esophagram, postero-anterior view, performed on May 23, 1949, shows the dilated and tortuous esophagus.

b. Lateral view, same study.

c. Right anterior oblique projection showing marked U-shaped angulation of lower esophagus.

d. Detailed enlargement of lower esophagus and stomach revealing S-shaped course of distal esophagus, and smooth conical character of the obstructing lesion.

SUMMARY

A case of cardiospasm is reported to demonstrate some of the difficulties encountered in arriving at a proper diagnosis. Although there have been reports of marked esophageal dilation which resembled enlargement of mediastinal lymph nodes, the presence of gastrointestinal symptoms usually has been stressed. The sequence of events in this case first suggested a bronchopulmonary infection. Inspection of the chest films obtained on admission caused a revision of opinion and a consideration of mediastinal disease. Evaluation of the earlier films confused the picture further by providing factual evidence that the mass had been present for some time. It was only when the gastrointestinal tract was studied incidentally that the actual cause of the symptoms was found.

It is suggested that diseases of the esophagus be considered in the evaluation of unexplained manifestations of the respiratory system.

SUMARIO

Cardioespasmo Simulando Tumores Múltiples del Mediastino

El caso de cardioespasmo comunicado sirve para poner de manifiesto algunas de las dificultades con que tropieza la formulación de un diagnóstico acertado. Si bien ha habido descripciones de pronunciada dilatación esofágica que semejaba patología de los ganglios mediastínicos, las historias clínicas recalcaban por lo general los síntomas gastrointestinales. El orden de los acontecimientos en el caso actual indicaban al principio infección broncopulmonar. La inspección de las radiografías torácicas tomadas al ingreso impuso una modificación de este parecer y la consideración de patología del mediastino. El estudio de las primeras radiografías enredó más el cuadro por aportar datos visibles de la presencia de una tumefacción benigna muy antigua. Sólo después de estudiar incidentalmente el tracto gastrointestinal fué que se dió con la verdadera causa de los síntomas.

Sugiérese que, al justipreciar las manifestaciones inexplicadas del aparato respiratorio, se tomen en cuenta las afecciones del esófago.

RESUME

Un cas de cardiospasme simulant des tumeurs médiastinales multiples

Un cas de cardiospasme présenté montre certaines des difficultés qui peuvent être rencontrées avant de parvenir à un diagnostic véritable. Bien qu'on possède des rapports sur des cas de dilatation oesophagienne marquée, qui suggéraient une atteinte des ganglions médiastinaux, les observations insistaient habituellement sur les symptômes gastro-intestinaux. Dans ces cas, la suite des événements a d'abord suggéré une infection bronchopulmonaire. L'examen des radiographies du thorax, qui ont été faites au moment de l'admission, ont fait réviser l'opinion première et la possibilité d'une lésion médiastinale a été envisagée. L'interprétation des films antérieurs compliquait encore plus la situation en nous montrant l'existence d'une masse qui n'avait pas évolué. Ce ne fut que lorsque le tube digestif eut été incidemment étudié que la véritable cause des symptômes a été découverte.

Il a été suggéré que les affections de l'oesophage soient prises en considération dans l'évaluation de manifestations inexpliquées du système respiratoire.

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SARCOIDOSIS (BOECK'S SARCOID) AND PREGNANCY[1,2]

KEITH P. RUSSELL

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Sarcoidosis is a disease of protean manifestations with considerable interest to the internist, dermatologist, radiologist, ophthalmologist, and orthopedist. Although studies of the disease have appeared with increasing frequency in the literature during the past decade, sarcoidosis has been largely of academic importance to the obstetrician and gynecologist. A survey of the English literature has failed to reveal any previous report of sarcoidosis in association with pregnancy. None of the standard textbooks dealing with obstetrics and obstetrical complications mentions the management of pregnancy in patients afflicted with this disease. These findings have prompted the report of a case in which both therapeutic abortion and a subsequent term pregnancy were associated with sarcoidosis.

In general, it appears unlikely that sarcoidosis as a clinical problem would very often confront the obstetrician. The effects of pregnancy on sarcoidosis and of sarcoidosis on pregnancy have apparently not been observed sufficiently in the past to warrant reporting. Nevertheless, the occurrence of sarcoidosis in females with frequency equal to that in males and its more common incidence in the childbearing years between fifteen and forty would indicate that the problem of management of pregnancy complicated by the disease would occasionally arise. Longcope (1) has reported a case of sarcoidosis involving the endometrium, discovered in a twenty-nine-year-old woman on whom a curettage was performed for uterine bleeding. She was well subsequently. The mediastinal lymph node enlargement which she also exhibited gradually disappeared. Harrell (2) mentions two patients who had had miscarriages and children who died soon after birth, but draws no inference that there was any connection between these occurrences and sarcoidosis. It therefore appears pertinent to report the following case in which proved sarcoidosis occurred in conjunction with two successive pregnancies, one of which was terminated by therapeutic abortion for this disease.

CASE REPORT

The patient, Mrs. A. G. C. (No. 45625), a white female, was first seen in 1939 at the age of twenty-seven when she suffered a spontaneous abortion. In 1940 she had a complete physical examination as part of an infertility investigation, at which time her chest was found to be clear and her nose and throat normal. Two small cervical nodes were palpated in the right posterior chain. Findings on pelvic examination were normal except for an uncomplicated retroversion. A Rubin test at this time indicated patency of the tubes. She subsequently became pregnant and delivered a normal female infant in May 1941. Her pregnancy was uneventful throughout. Routine blood and urine examinations revealed no abnormalities.

In November 1941 she was found to be again pregnant. Physical examination at this time revealed essentially normal findings. The chest was clear to percussion and auscultation. A routine tuberculin test with 1:5,000 OT (Mantoux) on November 21, 1941 was negative. The patient again had an uneventful prenatal course and delivered spontaneously a normal female infant in March 1942.

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[1] From the Department of Obstetrics and Gynecology, The Moore-White Clinic, Los Angeles, California.

[2] Aided in part by a grant from The Moore-White Medical Foundation.

In 1947 she returned because of secondary sterility, and in May the cervix was cauterized. Except for chronic cervicitis and uterine retroversion, the pelvic findings were again within normal limits. On February 19, 1948 the patient was found to be pregnant, the date of the last menstrual period being December 1, 1947. The uterus corresponded to the size of a two months' pregnancy, the adnexal areas were negative, and the cervix was smooth. A chest roentgenogram, taken that day as part of the routine prenatal study, revealed for the first time extensive pulmonary findings. There were soft, patchy infiltrations of marked degree throughout the whole of the right and left lung fields (figure 1). These appeared to occur primarily in the perihilar regions and extend outward toward the peripheries. No pleural reaction was noted. No cardiac abnormality was noted, and the bones of the thoracic cage appeared to be normal. The first impression of the radiologist was that these changes were of probable tuberculous etiology, but the manner of spread indicated that coccidio-

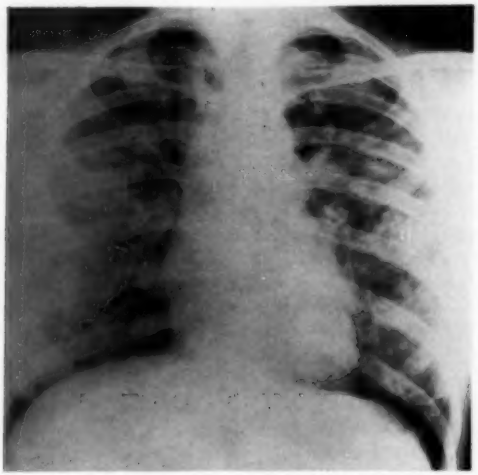

FIG. 1. Initial chest roentgenogram (February 19, 1948) showing extensive infiltration of both lung fields.

idomycotic infection should be excluded. The patient was referred for consultation with an internist. Examination revealed generalized lymphadenopathy, most pronounced in the right axilla; the nodes were soft and discrete. The remainder of the physical findings were noncontributory. The skin and eyes were uninvolved. Laboratory examinations revealed no abnormalities except for an elevated erythrocyte sedimentation rate of 36 mm. in one hour. There was no eosinophilia. Serum proteins were as follows: albumin, 4.1 gm. per 100 cc.; globulin 2.9 gm. per 100 cc.; total protein, 7.0 gm. per 100 cc. Tuberculin (1:5,000 OT, Mantoux) and coccidioidin tests were negative. The patient was then sent into the hospital for excision of an axillary lymph node for biopsy. Histologic examination of this tissue showed the typical findings of sarcoidosis (figures 2 and 3). Special stains revealed no acid-fast organisms.

Notwithstanding the extent of the pulmonary findings, the patient exhibited no constitutional reaction of any moment except mild fatigue. There were no complaints specifically referable to her pregnancy. Roentgenograms of the hands revealed no evidence of involvement of the bones by the sarcoidosis. Another chest film, however, taken two weeks after the initial film, showed some increase in the density of the pulmonary lesions (figure 4). A review of the case by three internists resulted in a recommendation that the pregnancy

be terminated. This was based on the extensive involvement of the lungs, the possible tuberculous etiology in sarcoidosis, and the occasional finding of fulminating tuberculosis becoming superimposed on cases of this type. It was not believed that sterilization should necessarily be done at this time because of the uncertain future course of the disease and the possibility that regression might take place, permitting future pregnancies. A dilatation and curettage was subsequently performed on March 24, 1948. Microscopic examination of the fetal elements, in addition to the chorionic and decidual tissues, revealed no histologic evidence of sarcoidosis.

The postoperative course was entirely uneventful. The patient continued to feel well, and pelvic examinations revealed normal involution. A chest roentgenogram obtained one month after termination of the pregnancy showed evidence of regression of the pulmonary infiltration (figure 5). The lesions appeared to be somewhat less dense, especially on the

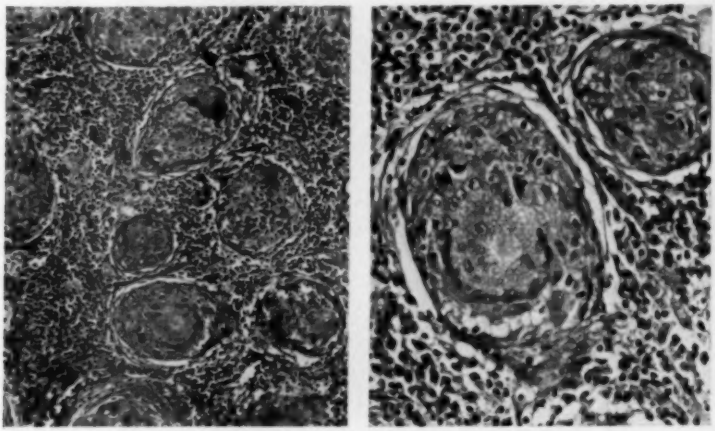

FIG. 2. (Left) Photomicrograph of axillary lymph node biopsy, showing characteristic multiple, discrete granulomata.

FIG. 3. (Right) Higher magnification of section shown in figure 2.

left. In September 1948, six months following termination of the pregnancy, the patient reported that, in spite of contraceptive measures, she had missed her menstrual period. She was found to be again pregnant, the last menstrual flow being in August. A repeated chest plate taken at this time revealed a definite improvement in the degree of infiltration (figure 6). Physical examination again revealed no abnormalities. The lymphadenopathy had largely subsided. Hematologic studies and urinalyses were normal. There was no eosinophilia.

The pregnancy was allowed to progress under close observation and the patient pursued an essentially normal course. Her weight gain totaled twenty-one pounds, blood pressure readings averaged 120 systolic, 70 diastolic in mm. of mercury, and the urine was consistently negative. No respiratory embarrassment occurred at any time. Roentgenographic examination of the chest during the eighth month of pregnancy showed a continuation of the improvement previously noted. There was marked reduction in the extent and density of the infiltration in both lung fields (figure 7). The patient delivered spontaneously a viable female infant in May 1949.

The newborn was found to show no evidence of sarcoidosis, and the placenta was normal. Postpartum blood count revealed a mild hypochromic microcytic anemia for which iron

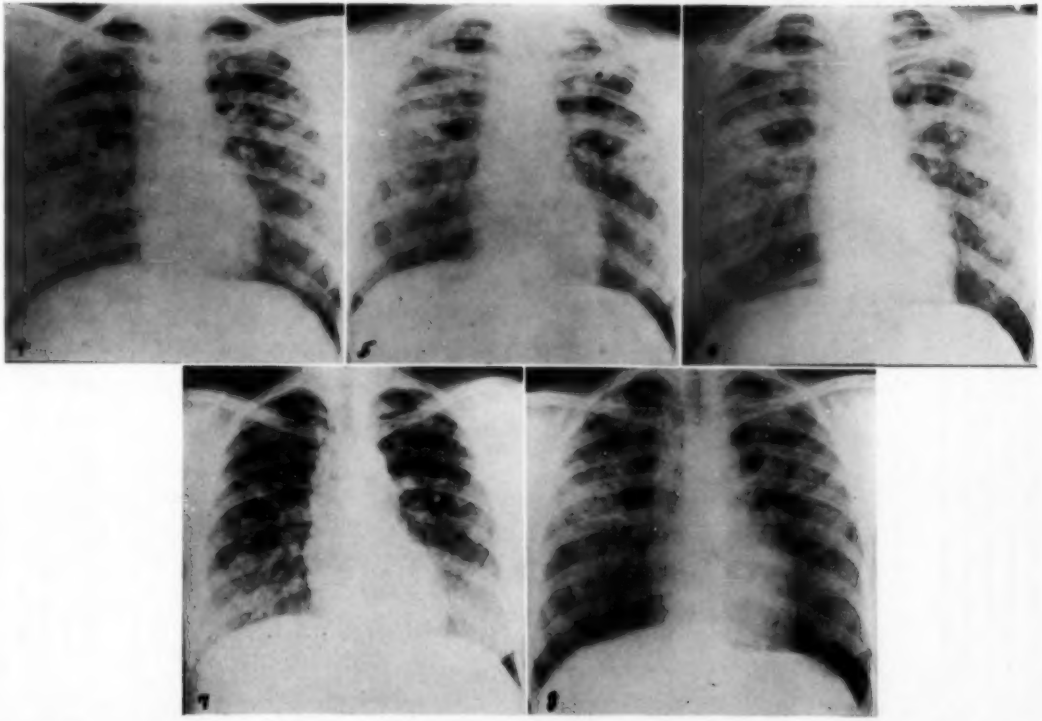

FIG. 4. Repeat film (March 5, 1948) taken two weeks after figure 1, showing some increase in density of the lesions.

FIG. 5. Chest film taken one month following termination of pregnancy (April 26, 1948). There is evidence of regression in the extent and density of the infiltration, especially on the left.

FIG. 6. Chest film taken six months following therapeutic abortion (September 23, 1948). There is definite improvement in the degree of infiltration.

FIG. 7. Roentgenogram of chest toward the end of eighth month of pregnancy (April 19, 1949). There is marked reduction in the extent of involvement over that seen at the beginning of pregnancy.

FIG. 8. Film taken nine months post partum (March 8, 1950), showing essentially the same degree of involvement as that toward the end of pregnancy.

was prescribed. After an uneventful puerperal course the patient was discharged from the hospital on the fifth postpartum day. Examination in six weeks revealed essentially normal pelvic findings. Nine months following delivery, a chest roentgenogram (figure 8) showed basically the same degree of pulmonary involvement as had been present in the film taken during the third trimester. One year following delivery, the patient stated that she continued to feel well and suffered no tiredness or other complaints. No cough, fever, or other constitutional reaction were present.

COMMENT

It seems reasonable to conclude from a study of the above case that pregnancy did not exert a deleterious effect on the course of the sarcoidosis. It also appears equally reasonable, however, that the termination of the first pregnancy was beneficial to the patient during what might be termed an acute phase of sarcoid involvement of the chest. At least, there was definite improvement in the roentgenographic features of the disease shortly following the therapeutic abortion. The usual chronic course of the process seemed to be somewhat ameliorated by the procedure. Improvement continued through the subsequent pregnancy to a definite degree.

There was no evidence that sarcoidosis had a detrimental effect on the pregnancy. No bleeding or other untoward symptoms occurred in either gestation, the patient pursued an essentially uneventful course throughout and following her pregnancy, and the infant presented no detectable abnormalities. The placenta did not exhibit any findings indicative of sarcoid involvement.

The role of therapeutic abortion in sarcoidosis remains an individual problem. If the sarcoid involvement is extensive and progressive, such termination of pregnancy may be indicated. In general, however, it seems unlikely that the usual chronic and benign course of sarcoidosis would be of sufficient severity in most cases to jeopardize the life of the mother or the health of the offspring. The above reported case would indicate that although pregnancy may not have the beneficial effect on sarcoidosis that it does on many diseases, the two processes are neither necessarily incompatible nor mutually detrimental.

SUMMARY

Sarcoidosis and pregnancy occurring in conjunction are discussed, and a case is reported in which both therapeutic abortion and term pregnancy were observed during the course of the disease.

SUMARIO

Sarcoidosis (Sarcoides de Boeck) y Embarazo

Después de discutir la concomitancia de sarcoidosis y gestación, comunícase un caso en el que se observaron tanto aborto terapéutico como embarazo a término durante la evolución de la enfermedad.

RESUME

Sarcoïdose (Sarcoïde de Boeck) et Grossesse

La sarcoïdose et la grossesse se produisant en même temps ont été l'objet d'une étude et il a été communiqué un cas dans lequel on a pu observer un avortement thérapeutique et une grossesse à terme, au cours de l'évolution de la maladie.

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Editorial

The Time Factor in Studies of the Outcome of Chronic Disease

> It has been my humble endeavour, in this work, to follow the example of Louis, and, wherever it has been practicable, to reduce my observations to a numerical expression. Some writers object to the application of statistics to medical science, and prefer trusting to what they call experience. But experience, to be of value to any one besides the immediate observer, must be something capable of definite expression. Moreover, the mind is apt to attach to accidental occurrences an importance, which is at once expelled by an appeal to the 'force brutale de chiffres.'

The above quotation is taken from the preface of Murchison's *Treatise on the Continued Fevers of Great Britain*, written in 1862. In the present era of scientific medicine, with its emphasis on the necessity of controlled studies, accurate observation, and reproducible results, few will disagree with Murchison. And yet, in tuberculosis and other chronic diseases we have scarcely begun to make any adequate statistical assessment of the value of therapeutic measures. The difficulty is that problems which, in acute disease, do not arise at all or are easily dealt with become most vexatious in chronic diseases. The issue is not the desirability of reducing observations on chronic disease to a numerical expression, but how this can and should be done.

In evaluating a therapeutic agent a controlled study is always desirable. The alternative, a comparison of results with the new agent with those previously obtained, is acceptable only in diseases of consistent and predictable outcome and when response to the new agent is striking. For example, the introduction of streptomycin treatment of tuberculous meningitis produced such a sharp change in the previous uniformly fatal course of the disease as to leave no question of the immediate efficacy of the therapy.

In making a controlled study of a new treatment for an acute condition, rigid criteria for diagnosis and for inclusion of patients in the study are drawn up; the experimental and control populations are chosen in some random fashion, such as alternation of admissions. Treatment of both groups is identical except for the drug which is being tested; and, if possible, even the attendant staff are not told which cases are getting the new treatment. At some fixed interval after onset or hospitalization, the outcome is recorded in terms of case fatality rate, febrile period, period of hospitalization, frequency of complications, or some other measure of severity of illness. Patients are under observation throughout the course of their illness, and this period is so short that deaths from intercurrent diseases, time trends in mortality, and aging of the patients may be disregarded. There is usually no difficulty with patients being lost to observation before the termination of their illnesses. The chief problem is maintenance of controlled conditions until the test and control series are large enough so that one can be reasonably confident that the observed differences are not due to

chance. This is not to say that it is easy to conduct a good controlled study of an acute disease, but it is much easier than in a chronic disease.

Seldom have studies of this kind been made in tuberculosis. Nevertheless, in diseases of such unpredictable course as brucellosis, rheumatoid arthritis, or tuberculosis, the long road to a sound basis of therapy can be immensely shortened by a few critical experiments. One need only consider the long history of artificial pneumothorax to realize the truth of this assertion. The streptomycin studies carried out by the British Medical Research Council (Brit. M. J., October 20, 1948, *2*, 4582) and the Tuberculosis Study Section, National Institutes of Health (Long, E. R., and Ferebee, S. H.: Pub. Health Rep., November 3, 1950, *65*, 1421) are illustrations of well-planned controlled investigations in tuberculosis.

A more limited and more easily realized objective is to measure the outcome of the disease in a particular series of patients treated in a particular way. The physician who sets out to do this, intending no comparison between different methods of treatment, nevertheless finds that a comparison is implicit in the study; this comparison is with the general population from which his patients were drawn. He also finds that it is decidedly difficult to cope with the time factor. Such mistakes are often made, as computing the average period of survival in a series of cases when many of the patients are still living, and speaking of a ten-year follow-up period when only a few of the patients could have had as much as ten years' observation. The remainder of this discussion will deal with methods for expressing the outcome of chronic disease in a numerical way, and will necessarily be centered around the time factor.

Let us consider the problem of the thoracic surgeon who wishes to study the long-term survivorship in a large series of patients on whom lobectomies have been performed over the past ten years. We will assume that the selection of cases for this operation and the surgical technique employed have not materially changed over the period, so that we are willing to regard the patients operated on in 1950 as the same kind of patients who were operated on in 1941. The surgeon may wish to study separately the immediate postoperative mortality and the later mortality; and, if so, he will begin his long-term study at a point, say, eight weeks after completion of the operation and will include only those patients who survived this immediate period. We then have a few patients on whom there are ten full years of observation; some operated upon only within the past year, and many in between. Furthermore, at various points in the ten-year period some patients were dropped from the study because, while known to be alive to a certain date, they were untraced after that date. Thus, there are three possible reasons why a particular patient should be observed for less than the maximum period of ten years: he was untraced for a portion of the whole period; he was operated upon less than ten years ago; or he is known to have died during the period.

There are several ways of dealing with such problems. Obviously, the time element is important and must be allowed for, and expressed in, any statement of risk of mortality. Obviously, too, there are not enough patients followed a

full ten years to provide a reliable indication of the prognosis. One of the simpler ways is to disregard all patients operated upon less than, say, five years ago or lost track of within five years after operation, and to report the results exactly five years postoperatively on all patients followed for five years or more or who died within this period. The disadvantages of this method are that it fails to consider at all the experience of those who were observed for a shorter period than five years, and fails to take account of the experience, beyond five years, of those followed from five to ten years. The latter objection is met by tabulating separately the six-year mortality of those followed for six years, the seven-year mortality of those followed for seven years, and so forth. Here one probably finds that the numbers with which he is dealing are so small as to present considerable chance variation, and the need to consider the whole material in a single analysis becomes evident.

Another, and in many ways a better, method of dealing with these difficulties is to use the life-table approach. This technique has long been used by actuaries, but it will interest readers of THE AMERICAN REVIEW OF TUBERCULOSIS to know that, so far as the present writer is aware, Dr. Lawrason Brown was the first clinician to apply this method in a clinical follow-up study. Dr. Brown and a collaborator, E. G. Pope, published several reports on the initial follow-up studies at the Adirondack Cottage Sanitarium (now the Trudeau Sanatorium). One of the first of these reports, in 1904, utilized elements of the life-table procedure, but it was employed more extensively in a paper which Brown and Pope contributed to the *Zeitschrift für Tuberkulose* in 1908 (*12*, 206).

The method found some use in Europe but does not seem to have been tried again in the United States until Frost (Am. J. Pub. Health, *23*, 426) in 1933 called attention to its usefulness as an epidemiologic tool in tuberculosis studies. Since then it has been applied to many kinds of problems. A detailed explanation of the technique would be inappropriate here; it has been outlined by Frost (Am. J. Pub. Health, *23*, 426), Puffer (*Practical Statistics in Health and Medical Work*, McGraw-Hill Co., Inc., New York, 1950), and Berkson and Gage (Proc. Staff Meet., Mayo Clin., 1950, *25*, 270). A brief description of its application to the problem just considered will be given.

The surgeon combines the first postoperative year's experience of all his patients, regardless of whether the operation was performed in 1941 or 1950. He records the number of persons under observation at the beginning of the year (here we are speaking not of a calendar year but a year of observation dated from the operation). He next determines the number of patients on whom observations terminated during that year, either because of failure to keep them under observation or because the experience is being analyzed before they can have a longer observation period. For example, patients operated on in October 1950 would necessarily be recorded as "withdrawn within one year" if the analysis were made as of July 1951. Deaths occurring during the observation year are next set down, deaths resulting from the disease under treatment being distinguished from those due to other causes. The number of patients who remained under observation at the beginning of the second postoperative year and the number of withdrawals and deaths during the year are next determined, and so on for as long a period as the patients still under observation constitute

a sufficiently large proportion of the original group. From this the surgeon can calculate the death rate and probability of dying for each observation year (these two rates are not quite the same thing) and the cumulative probability of surviving over any specified number of years after operation.

If, in addition to a knowledge of probabilities of survivorship in the group observed, it is desired to compare its mortality with that of the general population, this too can be done. The number of "person-years" of life experience contributed by persons in each sex and age group is determined, and the mortality rates of the appropriate general population group (obtained from official vital statistics reports) are applied to them in order to obtain the expected number of deaths. The assumption here, which has been shown to be reasonably valid, is that the total number of deaths among 1,000 persons observed for one year would not differ from the number among 200 persons observed for an average period of five years each. The observed and expected deaths may be compared, both with respect to deaths from all causes and those attributed to the disease under consideration.

The life-table method involves several assumptions which should be recognized because in some situations they cannot be justified. One is that those persons on whom observations are cut short at some point (for either of the reasons explained above) thereafter had a life experience similar to the persons who were followed. One can never make this assumption with entire confidence, but a comparison of the "lost to observation" group with those who remained under observation, with respect to various characteristics pertinent to the study, is reassuring if it reveals no major differences. Obviously, the fewer persons actually lost to observation, the better. Another assumption inherent in the method is that withdrawals from observation and deaths are more or less uniformly distributed over the intervals of time in which they occur. This is a much less serious assumption, and its accuracy can usually be tested; the shortening of time intervals in the life-table will usually obviate any difficulty here.

The method has, as we have said, a variety of applications and modifications. In the first place, the "starting point" of the observations may be any of a variety of events such as discharge from the sanatorium, an operation, the date of diagnosis of a disease, or the beginning of familial contact with a case of tuberculosis. It may be a point in calendar time, or it may be a specified age, in which case successive years in the life-table represent successive years of age rather than years since a specified event, and the probabilities computed are probabilities of survival from one birthday to the next. The end point, the frequency of which is to be measured, may be, not death as in our illustration but development of clinical tuberculosis or of a positive tuberculin reaction; progression of tuberculous disease; or "conversion" of sputum. Thus, the method is suitable for epidemiologic as well as clinical studies.

It should be strongly emphasized, however, that the end point must be a defined event capable of recognition by an objective test and that the validity of the findings will be proportional to the reliability with which the end point has been measured. It would not be possible to make "arrest of disease" the end point of a life-table study on tuberculosis, because this event cannot be sufficiently well defined or oriented in time. When the development or progression

of pulmonary tuberculosis, as revealed by serial roentgenograms, is the end point, several independent readings of each patient's series of films should be made, if possible, for it has been shown that the reproducibility of roentgenographic interpretations is not very high.

Whatever test is used to measure the end point should be applied at intervals so that the last negative and first positive observation will bracket a reasonably limited time interval; what this interval should be will depend on the disease and the end point being measured. In analyzing the data it may be desirable to employ time intervals of varying lengths; thus, if the risk of mortality following lobectomy is particularly high in the first postoperative year, the probability of survival may be computed for each quarter of that year.

The sanatorium administrator and clinician are both interested in the ways in which tuberculosis patients leave the sanatorium. For those patients admitted in a given period of years (some of whom will presumably still be in the institution at the time of the study) one can estimate the concurrent probabilities of dying in the sanatorium, of being discharged with medical approval, or of being discharged against advice by months from the time of admission as well as the cumulative probabilities of these three events up to any designated time. A knowledge of the periods in which the "hazard" of irregular discharges is concentrated may help to provide insight into the reasons for such departures and their control.

While this method provides a solution of some of the difficulties inherent in long-term studies, it must be emphasized that the *sine qua non* of a good follow-up study is good follow-up; that is, an energetic and unbiased attempt to obtain regular reports on the health of all discharged patients for as long a period as possible. To be well done, this usually requires advance planning and the participation of the medical social worker or public health nurse, as well as the cooperation of the patient, his family, and his private physician. It is better to make regular (perhaps annual) inquiries than to wait until the end of the study period and try to obtain information on all ex-patients, and it is especially important to avoid the bias of listing patients as "untraced" when the real reason for their disappearance is death or admission to another institution because of progression of disease. Regular contacts with some member of the patient's family and a periodic search of hospital records and death certificates help to avoid this bias.

The question of when to terminate the observations and report on the findings is another difficult one. In a disease like tuberculosis one does not have a really complete and trustworthy picture of the outcome unless he has followed all of the cases from onset to the death of the last surviving member of the group. Since the student of the disease is himself mortal, this is a counsel of perfection. We must depend, for the advancement of medical science in this field, upon the accumulation of many limited or even fragmentary studies. We can and should, however, expect that the time element will be properly handled in such studies. Statistics do have the "force of numbers," and it is necessary to guard against their improper use or misinterpretation.

PHILIP E. SARTWELL

NOTES

HARVESTING AND DISPENSING APPARATUS FOR BCG VACCINE

The traditional Calmette method[1] for harvesting cultures of BCG is based on the assumption that a 21- to 30-day-old 150 ml. Sauton BCG culture yields 5 gm. semi-dry weight of bacillary mass. Laboratories desiring a more constant concentration of BCG vaccine resort to transferring the bacterial mass to filter paper and to pressing out the excess liquid. The material is then transferred to a sterile porcelain crucible in which it is weighed. Finally, it is transferred to a flask containing stainless steel balls. After homogenization and dilution, the vaccine is aspirated into pipettes and dispensed into vials. The procedure invites contamination and is poorly adapted to the preparation of large amounts of vaccine.

In 1944[2] the writer described a harvesting apparatus that facilitated the preparation of vaccine and greatly reduced the incidence of contamination. Harvesting, measuring, and homogenizing were all performed in a closed system. A nomogram converted into grams the height of the semi-dry BCG column within the cylinder (figure 1). In 1945[3] a mechanism was added that delivered the required amounts of vaccine into vials. The apparatus was further improved in 1949[4] to include two glass cylinders, one for the transcutaneous and the other for the intracutaneous concentrations of vaccine. By means of switch-cocks, this apparatus delivered either concentration of vaccine from a common delivery spout. We experienced some difficulty, however, in constructing a suction system which would deliver the heavy concentrations of vaccine into the dispensing cylinder. The present apparatus accomplishes this and permits one person to fill, stopper, and seal eight to ten vials of BCG vaccine per minute.

The apparatus is constructed of stainless steel and standard Pyrex glass cylinders[5] (figures 2 and 3). Its case, in which it is sterilized, is also made of stainless steel and measures 15 by 11 by 18 inches. It is supplied with movable vents in the lid and lower front; these permit free circulation of steam within the case during autoclaving. A foot pedal connected with a central rod supplied with a lock nut adjusts the screw that controls the stroke of the syringe piston. Homogenization of the vaccine is accomplished by means of a hand crank or a Bodine 1/75-horsepower reduction motor making sixty cycles per minute.

KONRAD BIRKHAUG

DIVISION OF LABORATORIES AND RESEARCH
NEW YORK STATE DEPARTMENT OF HEALTH
ALBANY, NEW YORK
November 20, 1950

[1] CALMETTE, A.: L'Infection Bacillaire et la Tuberculose, 4th ed., Paris, Masson et Cie, 1936, p. 911-917.

[2] BIRKHAUG, K.: Indicateur de poids de vaccin BCG, Société scientifique de la tuberculose, Rev. de la tuberc., Paris, 1944-1945, *9*, 93; Vekt-bestemmer for BCG-vaksinen, Tidsskr. f. d. norske Nasjonalfor. m. tuberk., Oslo, 1944, *34*, 16.

[3] BIRKHAUG, K.: Kombinert apparat for høsting, oppslemming og tapping av BCG-vaksinen (Apparatus combining harvesting, homogenization, and dispensing of BCG vaccine), Tidsskr. f. d. norske Nasjonalfor. m. tuberk., Oslo, 1945, *35*, 20.

[4] BIRKHAUG, K.: Virulence and tuberculogenic studies of sixty consecutive weekly lots of BCG vaccine produced by standard technique, Am. Rev. Tuberc., 1949, *59*, 567.

[5] The apparatus is manufactured by the Boyntonville Machine Shop, Hoosick Falls, New York.

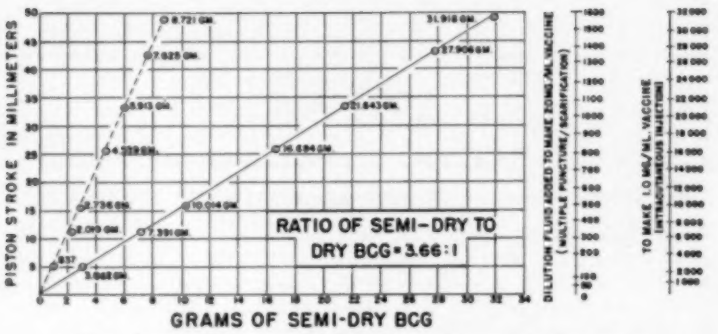
PISTON STROKE IN MILLIMETERS
RATIO OF SEMI-DRY TO
DRY BCG = 3.66 : 1
GRAMS OF SEMI-DRY BCG
DILUTION FLUID ADDED TO MAKE 20MG./ML. VACCINE
(MULTIPLE PUNCTURE/SCARIFICATION)
TO MAKE 1.0 MG./ML. VACCINE
(INTRADERMAL OR SUBCUTANEOUS INJECTION)

FIG. 1. Nomogram converting height of BCG column into grams

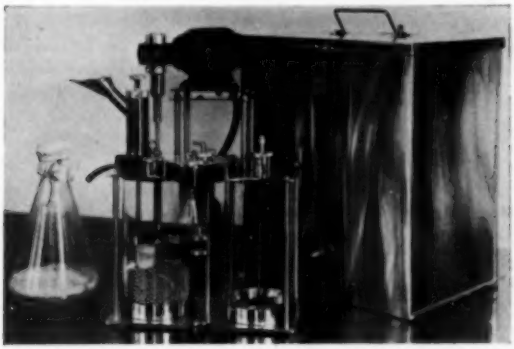

FIG. 2. Apparatus showing column of semi-dry BCG lying on top of steel balls in left cylinder. To the left, a 10-day-old Sauton culture of BCG; in the back, sterilizing case.

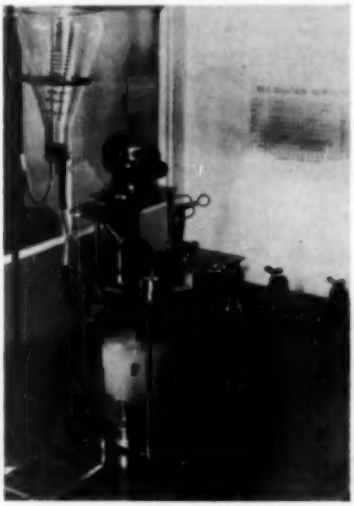

FIG. 3. Apparatus showing 20 mg./ml. BCG vaccine in left cylinder and 1.0 mg./ml. vaccine in right cylinder, with motor and diluting fluid flask in place.

Ernest S. Mariette

1888-1950

Dr. Ernest S. Mariette died on October 29, 1950, after a long illness. He was born on January 3, 1888 in Blue Earth County, Minnesota. He graduated from the University of Minnesota Medical School in 1913, and served his internship at the University of Minnesota Hospital. Following a period as Resident Physician at Nopeming Sanatorium, he came to Glen Lake, as Resident Physician, in January 1916, and in September 1916 was appointed Superintendent and Medical Director, a position he held until his retirement, November 1, 1949.

An outstanding administrator, Doctor Mariette saw Glen Lake grow from a fifty-bed cottage-type institution to a multi-storied hospital with a capacity of 675 beds. With facilities and equipment to provide complete medical and surgical care, it is not surprising that Glen Lake was the first sanatorium to be approved by the American College of Surgeons in 1927.

Doctor Mariette had a keen understanding of the fundamentals of the treatment of tuberculosis. He recognized that bed rest was the basis for all treatment, but he was constantly alert to the value of special forms of therapy. In addition to providing the best medical and surgical care, ancillary services were provided, such as medical social service, occupational therapy, library facilities, and adult education. All these services were coordinated with the rehabilitation program, a field in which Doctor Mariette was a recognized leader.

Doctor Mariette was Assistant Professor of Medicine and a member of the Faculty of the Graduate School of the University of Minnesota. In this position, he was fully aware of the teaching opportunities that were available at Glen Lake Sanatorium for professional hospital personnel, and under his leadership affiliations were made that would permit students of medicine, nursing, dietetics, and occupational therapy to come to the Sanatorium for some of their training. Also through his efforts, the Sanatorium was approved for fellowship training by the American Medical Association and before and since that time many physicians from at home and abroad have come to Glen Lake for study. Doctor Mariette contributed more than sixty articles dealing with tuberculosis to the medical literature.

He was active in many organizations, serving as Director of the National Tuberculosis Association during 1927–1928 and from 1935 to 1941. He also was President of the Mississippi Valley Conference on Tuberculosis, Mississippi Valley Trudeau Society, Minnesota Sanatorium Association, Minnesota Hospital Association, and Hennepin County Tuberculosis Association. He was a member of the Federal Security Agency, Office of Vocational Rehabilitation, Washington, D. C., from 1944 to 1948. He was a Fellow of the American College of Hospital Administrators, a Fellow of the American College of Physicians, and was certified by the American Board of Internal Medicine.

Possessed of a dynamic personality and great qualities for leadership, Doctor Mariette worked unremittingly for whatever he set out to accomplish. As he

struggled with deficits, brought on by rising costs, he refused to compromise on service. When it was suggested to him that some services might be curtailed or abolished, he replied with characteristic directness that he was "not interested in operating a second-rate institution."

Ernest S. Mariette
1888-1930

On June 9, 1923, Doctor Mariette married Anna Jones, of Minneapolis, who survives him. He also leaves a daughter, Grace, of Wayzata, Minnesota; a son, Edward, and three grandchildren of Glen Lake, Minnesota; and a brother, Percy A., of Arlington, N. J. They, with a host of friends, have suffered a great loss in his untimely death.

PETER M. MATTILL

AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

CURRENT STATUS OF ANTIMICROBIAL THERAPY IN TUBERCULOSIS

Report of Clinical Subcommittee of Committee on Medical Research and Therapy

Since the last report of this committee on the use of antimicrobial agents in the treatment of tuberculosis[1], there have been further developments, some of which are important enough to justify a new report. .

GENERAL PRINCIPLES

Although antimicrobial agents are accepted generally as important in the treatment of many forms of tuberculosis, much remains to be learned about their proper use. However, there are a number of general principles which are accepted by most students of the chemotherapy of tuberculosis. The most important of these are:

1. Drug therapy alone is not adequate treatment of tuberculosis.
2. The administration of antimicrobial agents should be carefully correlated with an over-all program of medical and surgical treatment.
3. Usually this should be done in a tuberculosis hospital or the tuberculosis division of a general hospital.
4. The emergence of drug-resistant strains of tubercle bacilli may be delayed by the simultaneous administration of certain combinations of antimicrobials.
5. The best combination available today is one of the streptomycin drugs together with some form of para-aminosalicylic acid (PAS).

Other problems about which there is less agreement are:

1. The exact indications for the use of antituberculosis drugs.
2. The optimal dosage and duration of treatment.
3. The clinical significance of the isolation of a drug-resistant strain of tubercle bacilli from a patient during treatment with that drug.

The clinical significance of the occurrence of drug-resistant strains of tubercle bacilli remains controversial. Although tubercle bacilli may become resistant to other antimicrobial agents, streptomycin-resistant strains seem to be of the most clinical significance. PAS-resistant strains occur after a longer period of treatment and, if administration of PAS is stopped, the resistant strain frequently is replaced by PAS sensitive microorganisms in a few weeks. In contrast, streptomycin-resistant strains may occur after several weeks of treatment and are persistent, seldom being replaced by streptomycin-sensitive tubercle bacilli. However, isolation of a streptomycin-resistant strain from a patient does not indicate that all tubercle bacilli harbored by the patient are resistant to the drug. Consequently, some clinicians continue to administer a streptomycin drug in spite of the presence of the resistant strain, and recent reports suggest that this may be of some value to the patient, especially if the need for antimicrobial therapy is urgent.

[1] Current Status of Drug Therapy in Tuberculosis: Report of Clinical Subcommittee of Committee on Medical Research and Therapy of the American Trudeau Society, Am. Rev. Tubere., 1950, *61*, 436.

THE STREPTOMYCIN DRUGS

The streptomycin drugs, streptomycin and dihydrostreptomycin, remain the most satisfactory antimicrobial agents in the treatment of tuberculosis. Neither drug is clearly superior to the other in either therapeutic efficacy or lack of toxicity in the dosage recommended below for general use. Strains of tubercle bacilli resistant to one of these drugs are always resistant to the other, so simultaneous administration of both would be of no special value. Hereafter in this report, unless otherwise specified, the word "streptomycin" will be used to refer to either of the streptomycin drugs.

Clinical studies have demonstrated that administration of 1 gm.[2] of streptomycin intramuscularly to the average adult with tuberculosis (12 to 20 mg. per kg. of body weight) every second or third day is apparently as effective as daily administration of the same dose. This intermittent regimen is less expensive and produces fewer toxic reactions and fewer strains of drug-resistant tubercle bacilli. Therefore, the committee recommends that an intermittent regimen be used whenever streptomycin is to be given to a patient for tuberculosis, except for more serious forms such as miliary and meningeal tuberculosis in which daily treatment is advised.

Although streptomycin may produce damage to the kidneys, drug fever, and dermatitis, the most serious toxic reactions have been vestibular and auditory damage. Drug fever and dermatitis seem to be allergic reactions and have occurred more frequently when regular streptomycin is used. They may be controlled by desensitizing the patient with increasing doses of regular streptomycin or by changing to dihydrostreptomycin. The neurotoxic reactions to streptomycin seem to be related to the occurrence of too great a concentration of the drug in the body fluids due to administration of too much of the drug per day or to impairment of function of the kidneys through which these drugs are excreted. For this reason renal function should be measured before treatment with streptomycin is begun and the dose decreased if function is impaired. Early detection of a neurotoxic reaction and discontinuance of treatment with streptomycin may prevent serious damage. For this reason vestibular and auditory functions should be tested before treatment and at intervals of one to two months during treatment.

Another antimicrobial agent should be given along with streptomycin to prevent or delay the emergence of streptomycin-resistant strains of tubercle bacilli. PAS is accepted generally as the most satisfactory drug for this purpose.

PARA-AMINOSALICYLIC ACID

Para-aminosalicylic acid (PAS) is an effective antituberculosis agent when given alone, although less effective than streptomycin. Usually it is given along with streptomycin to prevent or delay the emergence of streptomycin-resistant strains of tubercle bacilli. It should be given daily even though streptomycin is administered only two or three days of each week. The optimal dose is not known, but a daily dose of 12 gm. divided into

[2] Children often require relatively higher doses of streptomycin than adults, more than 20 mg. per kg. often being given. In one large clinic the following schedule has been employed safely and effectively:

Weight of child, pounds	*Gm. per day*
Under 10	0.30
10 to 19	0.40
20 to 39	0.50
40 to 59	0.60
60 to 89	0.75
90 and over	1.00

three or four doses is considered satisfactory. There is no single form of the drug which is acceptable to all, but most patients have less gastrointestinal distress when the sodium salt of PAS is given rather than the free acid. This may be prepared from the free acid as needed[3], or powder, tablets, or granules of sodium PAS may be used. When sodium PAS is given, the daily dose should be increased sufficiently to equal 12 gm. of PAS.

Daily doses of more than 12 gm. of PAS probably would have a greater therapeutic effect, and attempts have been made to administer as much as 24 gm. daily, but few patients tolerate this dose. In fact, most patients have some gastrointestinal distress when given 12 gm. daily and have to omit one or more doses from time to time or even discontinue use of the drug altogether for a few days. If daily administration of PAS is not tolerated, it may be given on two or three days of each week along with streptomycin, as this will delay, at least to some extent, the emergence of streptomycin-resistant strains of tubercle bacilli. However, every effort should be made to achieve daily administration.

A new compound, Benemid, (*p*-[di-n-propylsulfamyl]-benzoic acid) has been reported to delay the excretion of PAS, but general adoption of the drug is not warranted at this time.

Sodium PAS may be given parenterally when oral administration is not possible or when a large daily dose is advisable, for example, for patients with tuberculous meningitis. Vials containing either 5 or 15 gm. of PAS as a lyophilized sodium PAS powder are available. This may be given either subcutaneously or intravenously after dissolving in sufficient 5 per cent solution of dextrose in water to make a 1 per cent solution for hypodermoclysis or a 3 per cent solution for venoclysis. The solution is unstable and should be used within twenty-four hours after preparation.

PAS may be given alone in the treatment of infections due to streptomycin-resistant tubercle bacilli. In addition, some authorities recommend PAS alone during that phase of antituberculosis chemotherapy when preservation of the streptomycin sensitivity of the tubercle bacilli is of paramount importance; for example, in the early period of the long-range preparation of some patients for a resectional operation. Others use PAS alone for symptomatic relief of patients with incurable tuberculosis, the course of which is likely to be protracted.

Drug fever and dermatitis occasionally occur during administration of PAS. These may be controlled in some cases by desensitization of the patient with increasing doses of PAS. At other times it may be necessary to change to one of the other drugs such as amithiozone.

OTHER DRUGS

Thiosemicarbazones: The best known of these is amithiozone (4-acetylaminobenzaldehyde thiosemicarbazone), also known as TB 1. Amithiozone is an antimicrobial agent of relatively low effectiveness, probably less than that of PAS. It is chiefly used when PAS is not well tolerated, either with streptomycin or alone against a streptomycin-resistant infection. The recommended daily dose is 100 to 150 mg. Daily doses of 200 mg. frequently cause nausea, vomiting, and diarrhea. Continued administration of this dose may lead to anemia, granulocytopenia, and damage to the liver, particularly in patients with pre-existing hepatic damage. These changes usually are reversible and subside after use

[3] The following preparation is suggested: Add 50 gm. of $NaHCO_3$ and then 100 gm. of PAS to sufficient water to make a total volume of 500 ml. in a vessel sufficiently large to permit effervescence. Five milliliters of the resulting solution will contain 1 gm. of PAS. Since there is rapid deterioration in such a solution, it should be refrigerated and not used more than forty-eight hours after preparation. Flavoring may be useful.

of the drug has been discontinued. Obviously the blood and the function of the liver should be studied before, and repeatedly during, administration of amithiozone. It has been recommended that treatment be continued for eight to twelve months.

Sulfones: Diaminodiphenylsulfone and several derivatives of it are effective against experimental tuberculosis in animals. Several of these compounds have been studied clinically, but none has been satisfactory enough to warrant widespread use.

Neomycin is an effective antituberculosis agent, but its clinical use has resulted in serious deafness in a majority of patients. Therefore, its use is contraindicated.

Terramycin and viomycin: Preliminary reports indicate that both are effective against the tubercle bacillus *in vitro* and in experimental animals, but further controlled studies are needed before these drugs can be recommended.

Mycomycin is a potent antituberculosis agent, but in its present form is unstable. It is being studied in the laboratory but is not yet available for clinical investigation.

INDICATIONS FOR ANTIMICROBIAL THERAPY IN TUBERCULOSIS

Pulmonary tuberculosis and complications of pulmonary tuberculosis: The many types and combinations of types of pulmonary tuberculosis present multiple problems calling for considerable skill and experience in choosing the proper time and circumstances for employing drug therapy. Lesions of recent origin are more likely to respond than are lesions of long duration. However, there are some diffuse chronic disseminated lesions of long duration which are reversible. Cavitation usually requires collapse therapy or excision, and such forms of treatment are very frequently combined with drug therapy. Endobronchial tuberculosis is an indication for antimicrobial therapy, but the bronchial stricture which frequently follows healing is likely to require pulmonary resection; hence, a surgical procedure is frequently carried out after a short period of preoperative preparation. The other mucosal complications of pulmonary tuberculosis, including ulcerating lesions of the larynx, the oral cavity, and the gastrointestinal canal, frequently demand drug therapy even when the only goal attainable appears to be palliation of the distressing symptoms produced by such complications.

In the past, drug therapy has been withheld from most patients with minimal pulmonary tuberculosis and from those with acute tuberculous pleurisy with effusion because of the fear that the early appearance of drug-resistant bacilli might thwart later use of the drugs against more serious manifestations of tuberculosis. While this hazard still exists, it is greatly reduced when PAS is given along with streptomycin. Therefore, there is a growing trend to widen the range of indications to include these milder forms of tuberculosis when there is reason to fear that progressive disease is likely to develop. Factors of age, sex, race, and the many less tangible prognostic criteria are involved in making the important decision as to whether or not antimicrobial drugs should be employed in these manifestations of tuberculous infection. Similar issues are also met in dealing with primary or childhood pulmonary tuberculosis and in treating the patient with apparently stable pulmonary tuberculosis whose sputum occasionally contains tubercle bacilli.

Tuberculous empyema: Early detection of impending empyema and utilization of measures to obliterate the infected pleural space, combined with antimicrobial therapy, are necessary if surgical treatment is to be avoided. When resection of the diseased pleural membrane is necessary, antimicrobial therapy is advisable.

Tuberculous lymphadenitis: The appearance of tuberculous lymph nodes may represent but one phase of widely disseminated tuberculosis, and treatment should be planned accordingly. When suppuration has extended to the point of producing draining sinus tracts, drug therapy may yield an excellent local result. When subcutaneous cold abscesses are

detected, excision or drainage combined with the administration of streptomycin and PAS is the treatment of choice.

Tuberculosis of the genitourinary tract: The value of the surgical removal of necrotic foci combined with prolonged antimicrobial therapy is being confirmed by further experience. The use of PAS along with streptomycin has extended the duration of effective drug therapy, and one year of treatment is recommended for most of these patients.

Tuberculosis of the skeletal system: The well-established principles of surgical immobilization and excision of destructive bone tuberculosis have not been modified by the advent of effective antimicrobial therapy except to increase somewhat the applicability of surgical treatment. An exception appears to exist when the tuberculous process is detected while limited to the synovial structures, for rest plus antituberculosis drugs may be effective in such cases.

Unusual types of tuberculous disease: Tuberculous peritonitis, tuberculous pericarditis, and tuberculous otitis media respond to antimicrobial therapy when combined with other established therapeutic procedures.

Much remains to be learned about the proper selection of cases for treatment with antituberculosis drugs when dealing with cutaneous tuberculosis and "tuberculids." Similar confusion exists in treatment of the alleged tuberculous infections of the eye.

Miliary tuberculosis: This highly fatal type of tuberculosis continues to claim many lives despite the vigorous use of either streptomycin or PAS alone. It is believed that the incidence of relapse and of subsequent meningitis may be reduced by giving both drugs. Because of the critical nature of the disease many physicians prefer to overlook the toxic potentialities and give streptomycin daily at the rate of 20 to 60 mg. per kg. of body weight, and PAS in maximal tolerated doses orally or sodium PAS parenterally at the rate of 15 to 30 gm. daily. Treatment for many months, more than a year in some cases, may be necessary, a less intensive regimen being followed after the first four to six months.

Tuberculous meningitis: The high incidence of fatal relapse, even when an early remission is attained, has encouraged physicians to be most radical in the use of antimicrobial drugs when dealing with tuberculous meningitis. The amount of streptomycin and PAS should equal or exceed that advised above for treatment of miliary tuberculosis. There is even stronger indication for large amounts of sodium PAS given parenterally. Most physicians continue to use streptomycin intrathecally despite the frequently repeated objections to intrathecal injections of drugs. When streptomycin is given by this route, daily treatment should be given for the first week or ten days and then every two to three days for two to three months. Fifty milligrams is the usual dose, although some give as much as 100 mg. per treatment. Antimicrobial therapy should be continued for six months after clinical recovery or for a minimum of one year.

Use of antimicrobial agents at the time of operation for pulmonary tuberculosis: In spite of controversy about details, there is sufficient agreement about fundamental concepts to permit the following statements which can serve as guides to the use of antimicrobial agents in conjunction with the surgical treatment of pulmonary tuberculosis:

1. In the presence of sensitive tubercle bacilli, streptomycin is of great value in the prevention and treatment of tuberculous complications.
2. PAS should be given along with streptomycin to delay the emergence of streptomycin-resistant strains of tubercle bacilli.
3. The preoperative administration of sufficient streptomycin to produce streptomycin-resistant bacilli is justifiable only when this is necessary to salvage a patient who could not be prepared for operation in any other way.
4. In the presence of such resistant strains, tuberculous complications are more

frequent and more serious, and streptomycin is of questionable value in their prevention and treatment. However, surgical procedures should be performed when indicated, in spite of the presence of streptomycin-resistant tubercle bacilli, as the risk is not prohibitive. PAS is effective in these cases and should be given routinely, the parenteral routes being used if necessary.

5. For these reasons the over-all treatment should be planned so that the operation may be performed while the tubercle bacilli in the patient's sputum are still sensitive to streptomycin.
6. Preoperative treatment: The duration and amount of preoperative treatment varies according to the type and distribution of disease and the operation planned. It is used to accomplish the following: (a) reduction of the volume of sputum, as this reduces the chance of bronchial dissemination during operation; (b) resolution of the reversible component of the major focus of disease; (c) control of active disease in the contralateral lung; and (d) improvement of the patient's general condition.
7. Postoperative treatment: The use of antituberculosis drugs following operation depends on the estimated risk of tuberculous complications of the operative procedure used.

   In most clinics the drugs are not given in the case of thoracoplasty unless the patient is a substandard risk, as tuberculous complications following thoracoplasty are infrequent and usually respond to antimicrobial therapy. Furthermore, preservation of streptomycin sensitivity of the tubercle bacilli is desirable in case the thoracoplasty fails and pulmonary resection becomes necessary.

   Surgical procedures which traverse tuberculous tissue (resection, decortication, and cavernostomy) and those which create dead space in the body (pneumonectomy and extrapleural procedures) are definite indications for the use of antituberculosis drugs because of the frequency of tuberculous complications in the pre-antimicrobial era and the efficacy of the drugs in preventing these complications. However, there is no standardization of the amount or duration of treatment. Daily treatment may be advisable for a few days following operation, after which streptomycin may be given every second or third day until a total of 15 to 30 gm. has been given. PAS should be given daily as described above. When foci of active tuberculosis remain following these types of surgical procedures, the program of antimicrobial therapy should be planned accordingly.

DURATION OF THERAPY

There is a distinct tendency to prolong antimicrobial drug therapy in tuberculosis to, and well beyond, 120 days in many types of disease. This is an effort to exploit the fact that combined streptomycin and PAS therapy remains effective much longer than does either type of treatment alone, combined with a knowledge of the extremely chronic and relapsing nature of the pathologic process under consideration. It remains to be demonstrated conclusively that treatment may be continued for as long as one year with continued benefit, but there are some indications that such prolonged drug therapy may be justifiable occasionally when the clinical need continues to exist, and provided that other medical, surgical, and environmental therapeutic aids are being intelligently and aggressively brought to bear upon the problem simultaneously.

When prolonged therapy is employed the therapeutic regimen should be the one least

likely to lead to production of drug-resistant bacilli. At the present time the best regimen for noncritical types of tuberculosis is streptomycin administered every second or third day with PAS given daily as described in previous paragraphs.

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Notes

THE AMERICAN REVIEW OF TUBERCULOSIS AVAILABLE THROUGH MICROFILMS

University Microfilms, 313 North First Street, Ann Arbor, Michigan, have an exclusive contract with the National Tuberculosis Association to microfilm THE AMERICAN REVIEW OF TUBERCULOSIS, thus making past volumes available through microfilm service to libraries and other agencies with a minimum of storage space which desire to maintain reference libraries of the REVIEW. Even though the film is prepared at a high reduction ratio, it is remarkably clear and sharp and, when used with a reader which gives an enlargement of nineteen times or more, it is entirely satisfactory.

A microfilm is now available of Volume 59, 1949. The microfilms require a minimal amount of space for storage, being contained in a small cardboard box approximately two inches square.

COURSE FOR CHEST PHYSICIANS AND THORACIC SURGEONS

Temple University School of Medicine, Course in Broncho-Esophagology and Peroral Endoscopy. This course is especially planned for chest physicians and thoracic surgeons.

May 21 to June 1, 1951. Fee, $250.

Further information and application blanks will be sent on request.

Dr. Chevalier L. Jackson, 3401 North Broad Street, Philadelphia 40, Pa.

THE OXFORD CONFERENCE (1951) ON TUBERCULOSIS AND DISEASES OF THE CHEST

July 16–21, 1951

This conference, to be held during the Festival of Britain, has been called by the leading professional organizations in Great Britain.

It is designed to display thought and work on tuberculosis and diseases of the chest by men and women eminent for their work in this department of medicine, and to stimulate discussion.

Members of the Conference will be housed in Balliol, St. John's, and Trinity colleges, Oxford. The Conference will be accorded a civic reception by the Mayor of Oxford on the evening of July 16. The following three days, July 17, 18, and 19, will be devoted to lectures and discussions. On July 20, members will disperse to various thoracic centers throughout the country.

There will be social engagements, including a reception and dinner.

Communications may be sent to the Honorary Secretary, Dr. Stephen Hall, 16 Grosvenor Place, London, S. W. 1.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE (1952)

Preliminary Notice

President: Lord Horder

Vice-Presidents: Dr. Frank Howitt (Treasurer)

Dr. Philippe Bauwens (Chairman of the Executive Committee)

Honorary Secretary: Dr. A. C. Boyle

Address: 45, Lincoln's Inn Fields, London, W. C. 2

The Congress will be held in London from July 14 to July 19, 1952.

In accordance with the regulations of the International Federation of Physical Medicine, the meetings of the Congress will be reserved for matters dealing with the clinical, remedial, prophylactic, and educational aspects of Physical Medicine and with the diagnostic and therapeutic methods employed in Physical Medicine and Rehabilitation.

Technical, scientific, and historical Exhibitions also will be arranged.

In addition to the Scientific Programme, a full program of social events and entertainment is being planned for the members and associate members. Arrangements for London and provincial visits of scientific and historical interest are also being made for the Congress week and the following week.

This is a preliminary notice and full details will be notified later. Applications for the Provisional Programme should be addressed to the Honorary Secretary, International Congress of Physical Medicine (1952), 45, Lincoln's Inn Fields, London, W. C. 2.

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 63 MAY, 1951 ABST. No. 5

CLINICAL STUDIES, TUBERCULOSIS

Fascial or Muscle Tuberculosis.—Lesions referred to in the literature as muscle tuberculosis were in reality tuberculous lesions of the fasciae surrounding the muscles. The contractile tissues of muscles rarely show tuberculous lesions so that one may speak of an "immunity" of muscles to tuberculosis. The author observed 7 cases of tuberculosis of the thoracic wall. All of these patients originally had pleural empyema. Despite careful rinsing with procaine hydrochloride or with *p*-aminosalicylic acid (PAS), tubercle bacilli must have been carried into the thoracic wall. Approximately two weeks after thoracentesis a dense tumor appeared. Softening and abscess formation in the center of this tumor with formation of a fistula were observed later. After the empyema was cured, the fistula was extirpated and the muscles and fasciae were sutured in layers after instilling TB 1, PAS, and penicillin in the operative wound. Examination of the specimen disclosed fascial and not muscle tuberculosis.—*Uber traumatische Fascientuberkulose der Brustwand und ihre Behandlung, G. Hensel, Tuberkulosearzt, 1950, No. 9:522.—(E. Dunner)*

Calcified Hilar Nodes.—Benign hilar adenopathy has seldom been considered to produce symptoms. Too little emphasis has been placed on the effects of calcified hilar nodes. The chief clinical manifestations are partial bronchial obstruction with wheezing; partial or complete obstruction with the development of atelectasis, fibrosis, and infection accompanied by cough, sputum, and hemoptysis; bronchial erosion with the same symptoms plus expectoration of broncholiths; and endogenous spread of tuberculosis from a rupture of a tuberculous node into the bronchus. The first three may be indications for surgery. Of 8 cases of encroachment of hilar nodes against a bronchus there have been 6 with resection.—*The surgical aspects of calcified hilar lymph nodes, M. G. Buckles, Ann. Surg., 1950, 132: 972.—(W. H. Oatway, Jr.).*

Resection for Tuberculosis.—Two additional years of observation are reported on a group of 54 tuberculous patients surviving lobectomy or pneumonectomy. It is very striking that only 19 have remained well. Originally at least one-third had suffered a flare-up of activity; at present approximately two-thirds have manifested late activity of persistent foci of the disease. The pneumonectomy group showed a striking incidence of late tuberculous empyema. Although many of these patients again improved, 19 have died as a result of progression of the disease. The immunologic aspect of tuberculosis is important, and the disease cannot be entirely eradicated by extirpative surgery applied to the lung. The patients who had pneumonectomy fared better in so far as late results are concerned; 45 per cent have remained continuously well as compared with 24 per cent of the lobectomy group. Extirpative surgery should be disregarded, however, in pulmonary tuberculosis. The indications at present are (*1*) irreversible bronchostenosis with chronic infection and secondary bronchiectatic dilation, (*2*) lower lobe and occasionally middle lobe cavities, (*3*) persistent cavity after adequate thoracoplasty, and (*4*) possibly tuberculoma. Cases suitable for thoracoplasty are no longer considered for extirpation.—*Lobectomy and pneumonectomy in the treatment of pulmonary tuberculosis, R. H. Sweet, J. Thoracic Surg., February, 1950, 19: 293.—(R. E. MacQuigg)*

Pneumonectomy with Immediate Thoracoplasty.—In 10 patients pneumonectomy and rather extensive thoracoplasty were performed

at a single operation without mortality. The indications now include contralateral emphysema and expected postoperative pleural complications. One bronchial fistula occurred but prompt obliteration of the pleural space should lessen the dangers of fistula and empyema. Decostalization sufficient to permit the scapula to fall in supplemented by a pressure dressing appears to render the mediastinum relatively stable. The coughing mechanism in the immediate postoperative period appears to be enhanced. In the discussion of this paper, P W. Sanger stated that it is easier to perform the thoracoplasty first where resection and thoracoplasty are done together.—*Pneumonectomy followed by immediate thoracoplasty, R. K. Iverson & H. L. Skinner, J. Thoracic Surg., April, 1950, 19: 491.—(R. E. MacQuigg)*

Blood Volume Changes in Thoracoplasty.—There is a significant loss of blood between thoracoplasty stages, probably due to loss of sanguinous fluid into the operative wound space. Neither the hematocrit nor the total circulating plasma protein is an accurate indicator of the amount of blood lost or replaced. An increase in the circulating blood volume of 3 patients paralleled their clinical improvement.—*Blood volume changes in tuberculous patients treated by thoracoplasty, F. F. Allbritten, H. Lipshutz, B. J. Miller, & J. H. Gibbon, Jr., J. Thoracic Surg., January, 1950, 19: 71.—(R. E. MacQuigg)*

Sympathetic Block for Tension Cavities.—Many procedures have been used in an attempt to close tension-type pulmonary cavities. For those cavities remaining despite a satisfactory anatomical collapse, attempts have been made to close the cavity by reshuffling the amount of air in the pneumothorax space. Occasionally, cavities have been noted to close after abandoning the pneumothorax. Roloff and Götzky attempted to close cavities with pleura massage. Seidel used atropine and phenobarbital to affect the vagal tone. Straube and Kaufman reported results with acetylcholine electrophoresis. The intravenous use of 10 cc. of a 1 per cent solution of procaine has been advocated by others. The author injected 5 cc. of a 2 per cent solution of procaine hydrochloride at the level of the third to fourth rib and occasionally to the sixth rib three times a week. These injections were given for fifty-five days. Roentgenologic control examination revealed that the cavity had become smaller after sixteen days and was no longer detectable with laminagrams after thirty-seven days. Thus, a cavity that was refractory to various types of treatment for a period of eight months disappeared within six weeks in response to blockage of the thoracic sympathetic trunk. Three other cases are cited in which tuberculous cavities with stiff walls responded to blockage of the thoracic sympathetic trunk. A favorable influence is exerted by the predominance of the parasympathetic effects as a result of the exclusion of the antagonistic impulses from the sympathetic fibers.—*Sympathicus Blockade bei trägen Kavernen, S. Witte, Tuberkulosearzt, 1950, No. 9: 518.—(E. Dunner)*

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Löffler's Syndrome in Children.—The syndrome of benign transitory lung infiltration and eosinophilia described by Löffler was found in 8 children, 2 of whom had a longer course than usually described. All but one of the patients were Puerto Ricans in New York. Of the children, 5 had a typical picture; 3 were unusual and had a fine miliary mottling which persisted from seven weeks to seven months. The chronic cases also had disturbed liver function. All of the patients survived; in 7, the lung lesions cleared before the eosinophilia; and intestinal parasitism was present in 7.—*Pulmonary infiltration and blood eosinophilia in children (Loeffler's syndrome), R. L. Nemir, A. Heyman, J. D. Gorvoy, & E. N. Erwin, J. Pediat., December, 1950, 37: 819.—(W. H. Oatway, Jr.)*

Infantile Asthma.—A case of asthma and rhinitis is reported in a one-year-old infant with a strong family and personal history of

allergy. Passive transfer tests revealed positive reactions to tobacco and other antigens. Cessation of smoking by the mother resulted in complete relief of the child's symptoms for eighteen months (Authors' summary).—*Bronchial asthma due to allergy to tobacco smoke in an infant, F. L. Rosen & A. Levy, J.A.M.A., October 21, 1950, 144: 620.—(H. Abeles)*

Extrapulmonary Air in Newborn.—A case of aberrant air in an infant is added to the brief list of similar reports. The child was inadvertently born into a toilet. When examined a few hours later, he was cyanotic, had frothy sputum, and was breathing at a rate of 80 per minute. There were coarse dry and wet rales in the lungs. A massive subcutaneous emphysema was noted in the neck and scalp. A roentgenogram showed atelectasis of the right upper lobe as well as air in the neck, scalp, and anterior mediastinum. The condition improved over several days but oral feeding produced gagging and cough. An esophogram was normal but a left pneumothorax was present. The infant died after an oral feeding on the fifteenth day of life. At necropsy a tiny fistula in the wall of the left main bronchus was found.—*A fatal case of pneumomediastinum, subcutaneous emphysema, and pneumothorax lenta in a newborn infant, J. A. Ripp, J. Pediat., December, 1950, 37: 917.—(W. H. Oatway, Jr.)*

Subcutaneous Emphysema in Measles.—Three cases of measles in young children were complicated by the development of subcutaneous emphysema. Recovery in all 3 cases was uneventful. The rarity of this complication is noteworthy. The mechanism postulated to be responsible is the dissection of air via the lung root and mediastinum to the tissues of the chest wall and neck through some discrete ulceration of the bronchial mucous membrane in the respiratory tract within the lung.—*Interstitial emphysema in measles, J. J. Linehan, Brit. M. J., September 30, 1950, No. 4682: 762.—(E. A. Riley)*

Virus Pneumonia.—Apart from the epidemic forms of virus pneumonia, there occur severe, sporadic, nonseasonal virus pneumonias in the absence of other cases of mild disease of the respiratory tract. Multiple pneumonic cases may occur simultaneously or in succession in family groups. Whether the epidemic forms and the sporadic forms are etiologically the same still cannot be said since the cause of neither is known. Clinically, they are identical. Sporadic virus pneumonias give rise to diagnostic difficulties. They may be confused with pneumococcic atypical pneumonia, tuberculosis, typhoid fever, psittacosis, Q fever, ornithosis, coccidioidomycosis, and histoplasmosis. Over a three-year period, 7 such patients with severe virus pneumonia have presented diagnostic and therapeutic problems.—*Severe, sporadic virus pneumonias, diagnostic and therapeutic problems, H. A. Reimann, J.A.M.A., September 9, 1950, 144: 81.—(H. Abeles)*

Cavitation by Expectoration of Tissue.—The prompt appearance of a pulmonary cavity at the site of a previously visible metastatic nodule must be rare following the expectoration of a fragment of tumor tissue. An example is reported in a patient with Ewing's sarcoma of the femur and with pulmonary metastases seen by roentgenography and later confirmed at autopsy. Shortly after the chest film was taken the patient coughed up a fragment of pink tissue measuring 13 by 9 by 4 mm. A roentgenogram of the chest taken immediately after this incident revealed a rarefaction, interpreted as a cavity, at the site of a previously noted metastatic nodule. Microscopic examination of the tissue was reported as consistent with Ewing's tumor. Five months later the patient again expectorated a smaller mass of tumor tissue. At this time the additional cavitation could not be demonstrated radiographically. Soon thereafter the patient died. The autopsy revealed that the cavity seen in the earlier roentgenogram was largely occupied by metastatic tumor, and no cavity was demonstrable.—*Pulmonary cavitation following expectoration of neoplastic tissue, S. Dolgoff & R. H. Hansen, Am. J. Clin. Path., October, 1950, 20: 974.—(J. S. Woolley)*

Pulmonary Cavitation.—A 39-year-old man was hospitalized because of signs and symptoms of pulmonary disease. Roentgenograms of the chest showed multiple cavities and nodular densities with subsequent regression in some areas coincident with progression in others. The patient's course was characterized by widespread, bizarre symptoms indicative of disease in several organ systems. He had signs and symptoms of pulmonary disease, nephritis, hypertension, hemorrhagic cystitis, gastrointestinal disease with pain in the testis, joints and muscles of the legs. He failed to respond to treatment and he died after five and one-half months of hospitalization. The pathologic diagnosis was periarteritis nodosa with large cavitating necrosis in the lungs.—*Pulmonary cavitation due to polyarteritis, B. P. Sandler, J. H. Matthews, & S. Bornstein, J.A.M.A., October 28, 1950, 144: 754.*—*(H. Abeles)*

Treatment of Silicosis.—The static nature of silicosis and the reversible aspects of the complicating pulmonary conditions must be stressed in any consideration of therapy for this disease. Experience indicates that intermittent positive pressure breathing with the supplementary use of bronchodilator drugs and diaphragmatic elevation provides a definite means for pulmonary rehabilitation. It appears from the clinical and physiological evaluation of the treatments that the processes related to infection and the deposition of various dusts may outstrip the fundamental condition of silicosis in causing significant signs and symptoms. The roentgenograms have not been useful in judging the degree of improvement due to treatment. It appears that while silicosis is a progressive, disabling condition, a dynamic approach to therapy is indicated with reference to the rehabilitation of pulmonary tissue that is not totally involved in silica action.—*Pathological and physiological factors involved in the treatment of silicosis in coal miners, B. Gordon & H. L. Motley, Arch. Indust. Hyg. & Occup. Med., October, 1950, 2: 365.*—*(T. H. Noehren)*

Bronchial Asthma Therapy.—Twenty patients wth bronchial asthma were treated by the oral administration of a mixture of alkalis, consisting of 50 per cent sodium bicarbonate, 20 per cent calcium carbonate, 20 per cent sodium citrate, and small and variable amounts of potassium and magnesium sulfate. In the majority of the cases no asthmatic attacks occurred when the drug was given in divided doses over twenty-four hours. In a smaller number of cases the cough disappeared but milder and shorter attacks occurred. In some cases no effect was seen from this treatment.—*Behandlung des Asthma bronchiale mit peroralen Alkalien, L. Lazarovits, Wien. klin. Wchnschr., November 17, 1950, 62: 868.*—*(G. C. Leiner)*

Effect of Respiration on Pulse.—In normal persons the arterial pulse pressure increases during expiration and decreases during inspiration. In bronchial asthma there is an increase of this normal pattern. In several patients with severe left ventricular failure the pulse pressure was found to increase in inspiration and to fall in expiration. With recovery from the left ventricular failure change from the anomalous to the normal pattern was observed. The anomalous pattern is most likely due to engorgement of the pulmonary vessels.—*The effect of respiration on the arterial pulse in left ventricular failure, R. F. Maronde, H. E. Martin, J. P. Mechan, Jr., & D. R. Drury, Am. Heart J., December, 1950, 40: 930.* *(G. C. Leiner)*

Spontaneous Pneumothorax.—The prognosis in cases of spontaneous pneumothorax is generally favorable but serious complications may occur. The most frequent is recurrence, reported in 10 to 45 per cent of cases. Of the 8 cases reported here, 5 were recurrent. Recurrent attacks are so frequently mild that the incidence probably is higher than is generally assumed. If there is a one-way valvular action, tension pneumothorax may develop, as reported in 10 to 16 per cent of cases, and may result in death. Cases of bilateral tension pneumothorax have been reported and the

mortality rate is not negligible. In the present series, one patient developed pneumonia of the collapsed lung and pyopneumothorax. Another had tuberculosis which was being treated with artificial pneumothorax when a fatal contralateral pneumothorax occurred. When the diagnosis of spontaneous pneumothorax has been established, intrathoracic pressure should be measured. If the pressure is elevated or if the lung is totally collapsed, air should be aspirated until the pressure is zero. It may be necessary to carry out repeated aspirations or drainage under water. The drainage tube preferably should be inserted in the second or third intercostal space anteriorly. Drainage decreases the danger of disaster while further treatment is considered. Thoracoscopy is a safe enough procedure to use routinely in the diagnosis of spontaneous pneumothorax. It is now possible to undertake radical surgical treatment aiming at complete extirpation of the affected area. Such treatment is especially indicated in cases of chronic or recurrent attacks or of tension pneumothorax. Patients receiving operative treatment do not have to stay in bed for so long a period as those receiving silver nitrate injections. In 5 of the 8 present cases, resection of the affected area was carried out successfully.—*The treatment of simple spontaneous pneumothorax, P. C. Curti & T. Poulsen, J. Thoracic Surg., January, 1950, 19: 145.*—(*R. E. MacQuigg*)

Spontaneous Pneumothorax.—Chronic and recurring pneumothorax is being diagnosed in apparently healthy persons with increasing frequency. Approximately one case for every 1,000 students was found at the University of Virginia. Of a series of 30 cases of spontaneous pneumothorax at the Los Angeles County Hospital, one became chronic and 3 were recurrent. The incidence of chronicity and recurrence of the pneumothorax is reported at 2 to 13 per cent. In the largest series reported, 46 to 71 cases were chronic, while 25 were recurrent. In 14 of the author's 15 cases, a cyst, bleb, or bulla was found. Collapse remaining for three months after spontaneous pneumothorax is an indication for active therapy; bed rest is ineffectual in chronic cases. Since roentgenograms often fail to show the etiology, a similar condition may exist in the contralateral lung. Bilateral spontaneous pneumothorax is being reported with increasing frequency. The authors report a 23-year-old patient who developed spontaneous pneumothorax on the left following successful resection of four pulmonary blebs for a spontaneous pneumothorax on the right. Successful and functional re-expansion of the right lung after three years' pneumothorax saved his life when the left lung suddenly collapsed. Pneumonia in the uncollapsed lung has been a cause of fatality. Surgical procedures are preferable to the therapeutic production of chemical pleuritis; in 7 of 16 cases, a definite pleural membrane was produced by the pneumothorax and the production of additional pleuritis and pleural thickening would seem useless. Surgical methods include closed catheter drainage, phrenic paralysis, thoracoscopy with internal pneumonolysis, and thoracotomy with various surgical procedures. Catheter drainage is recommended only for certain poor risk cases. It is important to introduce the catheter in the second interspace anteriorly so that fluid or fibrin will not clog the tube. Phrenic paralysis is not recommended. Thoracoscopy is indicated for diagnosis and, when string-like adhesions are present, for therapy. In 2 instances the authors were able to divide adhesions and permit rapid healing of the pulmonary rent. Thoracotomy is preferred to thoracoscopy and was used in 13 instances. A pleural membrane was found in 6 cases; and in the 5 cases where removal was performed, rapid expansion followed. Maximal pulmonary function is preserved.—*The surgical management of chronic "spontaneous" pneumothorax, L. A. Brewer III, F. S. Dolley, & B. H. Evans, J. Thoracic Surg., February, 1950, 19: 167.*—(*R. E. MacQuigg*)

Pulmonary Embolism.—The incidence of fatal pulmonary embolism in routine and postoperative autopsies was studied. Among the sites of venous thrombosis the ovarian veins

were the source of emboli in only 0.6 per cent of the cases. In a series of 14 cases of pelvic vein lesions, 2 were due to phlebothrombosis and 12 to thrombophlebitis. The former caused few symptoms and no emboli to the lungs; all but one of the inflammatory lesions produced pulmonary infarction.—*Ovarian vein phlebothrombosis and fatal pulmonary embolism, W. A. Bailey, Ann. Surg., November, 1950, 132: 986.*—(*W. H. Oatway, Jr.*).

Segmental Resection.—Refinements in the operative technique have been used in 28 cases. There were no empyemas, 2 minor fistulas, and one death. In the discussion of the paper, R. R. Shaw stated that in bilateral bronchiectasis it is often advisable first to attack the less involved side. With this side free of disease the more diseased side can be attacked secondarily; if difficulties are encountered, a pneumonectomy could be performed. If such difficulties occur in attacking the more involved side first, nothing can ever be done about the disease on the other side. Glover commented that in tuberculosis so-called alveolar leaks frequently occur after segmental resection and must be treated with respect. Otherwise proper expansion of the lung will not occur, almost invariably leading to empyema with bronchopleural fistula. F. Hughes, Jr. and J. M. Chamberlain stated that the merit of segmental resection in tuberculosis had not yet been decided.—*Segmental pulmonary resection: Details of technique and results, R. H. Overholt, F. M. Woods, & B. H. Ramsay, J. Thoracic Surg., February, 1950, 19: 207.*—(*R. E. MacQuigg*)

Segmental Resection.—Segmental resection of a portion of a lung lobe may remove disease with minimal sacrifice of normal parenchyma if (*1*) the proper segment or segments are removed, (*2*) the residual circulation is not impaired, and (*3*) re-expansion is complete and immediate. The information gathered by postero-anterior and lateral laminagraphy is more reliable than that gained by the surgeon's palpation. Postoperative examination of the specimen more frequently coincides with the laminagraphic studies than with the surgeon's impression. The immediate morbidity rate of segmental resection is slightly greater than that of lobectomy. The operation takes longer, demands more meticulous dissection, and requires greater postoperative vigilance. The late morbidity figures, however, may prove to justify it because not only is the disease removed, but maximum pulmonary function is preserved.—*Segmental resection in pulmonary diseases, J. M. Chamberlain & T. C. Ryan, J. Thoracic Surg., February, 1950, 19: 199.*—(*R. E. MacQuigg*)

Surgery for Bilateral Bronchiectasis.—One-third of bronchiectatic patients have bilateral disease. Of 58 patients reported here, 43 had severe or moderately severe disease in both lungs; 27 have had unilateral and 31 bilateral operations. All of the 4 deaths followed surgery on the second side in bilateral resection; the last 18 consecutive bilateral resections were completed without a death. Gross disease has been considered an indication for operation provided the upper lobes with the exception of the lingual segment were healthy. Such patients have have all been improved by the first operation; sputum has usually been reduced by one-third or one-half; the patients have gained weight, and have felt better. Often it is tempting to accept such improvement and avoid the risk of a second operation but some of these patients relapse and all remain subject to the disability and dangers of residual bronchiectasis. The operative danger is due mainly to anoxia. A single contralateral lobe can carry a patient through an arduous second resection, provided the airway to that lobe remains clear. If the extent of the disease is different on the two sides, the lesser resection is done first so that there will be a larger functioning lung at the critical second operation. Six months appear to be the minimal desirable interval between stages. Breathing exercises are important in recovering function; inhalation of nebulized penicillin or streptomycin has not been useful. Thorough postural drainage is carried out immediately before the preoperative sedation; bronchoscopic suction is

done immediately after, and sometimes before, operation. Continuous oximeter observations of the arterial oxygen saturation have been made during operation in all cases since 1946. On 2 occasions operation was abandoned after freeing the lobe because anoxia could not be corrected. Both patients were satisfactorily operated upon later. None of the patients is unemployable because of respiratory disability. One man has gained forty pounds and is doing fairly heavy work as a steel worker although he has only his upper lobes without the lingula. Because of the high incidence of pleural complications and the tendency to develop bronchiectasis in the retained segment, segmental resection of all the basic divisions has been abandoned.—*The surgical treatment of bilateral bronchiectasis, F. G. Kergin, J. Thoracic Surg., February, 1950, 19: 257.—(R. E. MacQuigg)*

Bronchospirometric Studies of Lobectomy.—Pulmonary ventilation and oxygen uptake were determined in 64 patients whose bronchiectasis had been delineated by bronchography of all lobes, and compared with 63 normal individuals of the same age range. In 44 of the patients, lobectomy was done. In bronchiectasis it was found that the maximal breathing capacity was reduced in proportion to the extent of the disease mainly because the depth of respiration during maximal voluntary effort was decreased. Bronchospirometry showed that the oxygen uptake in the diseased lung was often reduced more than the volume of air moved, probably despite residual function in the diseased portions and compensation in the other segments. The reduction in the proportion of air moved by the diseased side was made up, in part, by relative increase in amount of air moved by the normal lung; the over-all ventilation was normal only during quiet respiration. Lobectomy or resection of diseased segments usually did not change the over-all ventilation to any extent. Often the maximal breathing capacity increased after resection and occasionally it decreased. Bronchospirometry showed that in 18 of 24 cases there was some further loss of function on the diseased side after surgical removal of diseased segments. These reductions were balanced by increased function of the opposite lung. In almost every case a reduction in the proportion of oxygen absorbed on the operated side was associated with some postoperative complication, such as empyema, atelectasis, or fever attributable to the chest lesion. Reductions in the proportion of air moved on the operated side occurred, on the other hand, following an apparently uneventful postoperative course. Postoperative complications such as atelectasis and fever attributable to the chest lesion may occur without changing the proportion of oxygen absorbed or the proportion of the air ventilated by the operated side.—*Bronchospirometric studies in bronchiectasis, before and after lobectomy, J. H. Long, C. M. Norris, W. E. Burnett, & M. R. Wester, J. Thoracic Surg., March, 1950, 19: 477.—(R. E. MacQuigg)*

Relationships After Pneumonectomy.—The adaptations to pneumonectomy were investigated in 16 subjects. The study included measurements of pulmonary flow and pressure and analysis of alveolar ventilation. In the absence of thoracoplasty, pneumonectomy is not inevitably followed by evidence of distention of the remaining lung. If pneumonectomy is complicated by pulmonary distention, thoracoplasty is advisable; but the final result depends to a great extent on the presence or absence of a pathologic process within the remaining lung. Thoracoplasty complicated by scoliosis may actually cause pulmonary distention.—*Pulmonary circulation and alveolar ventilation—perfusion relationships after pneumonectomy, A. Cournand, R. L. Riley, A. Himmelstein, & R. Austrian, J. Thoracic Surg., January, 1950, 19: 80.—(R. E. MacQuigg)*

Parasternal Omental Hernia.—Pneumoperitoneum is an accessory diagnostic aid in suspected parasternal omental hernia. The differential diagnosis of masses at the cardiophrenic angle involves lymphomas, teratomas, lipomas, neurofibromas, aberrant thyroids, celomic cysts, and peripheral lung neoplasms. In 3

cases various roentgen procedures were evaluated. With a barium enema the transverse colon often assumes an inverted "V" pattern pointing toward the foramen of Morgagni but there may be cases in which pneumoperitoneum will reveal positive information in spite of negative barium enema studies. There are certain cases in which none of the characteristic roentgen findings are present, making a definite preoperative diagnosis impossible.—*The roentgen manifestations of parasternal omental hernia, J. S. Stewart, J. Thoracic Surg., March, 1950, 19: 399.—(R. E. MacQuigg)*

Mediastinal Packing for Esophageal Varices.—In 8 cases severe bleeding from esophageal varices was treated by gauze packing of the posterior mediastinum. It was hoped that granulations would form containing a venous plexus as a safer shunt from the portal to the caval circulation. Portocaval and splenorenal anastomoses are more physiologic than other procedures but carry a high operative mortality. The evidence indicates that the packing technique does develop periesophageal collateral circulation. When subsequent hematemeses occur they are rarely as severe or profuse as before operation.—*Further observations on packing of mediastinum for esophageal varices, J. H. Garlock & M. L. Som, J. Thoracic Surg., April, 1950, 19: 572.—(R. E. MacQuigg)*

Funnel Chest and Allied Deformities.—Funnel chest is common and may be incapacitating. The deformity is produced by a short central tendon of the diaphragm so that the lower end of the sternum is drawn backward during inspiration. Its character is determined by the portion of the central tendon which is shortest. The lung is compressed but this seldom results in more than a 25 per cent reduction of the lung volume. The lung may be distorted and the respiratory infections to which these patients are unduly susceptible may be due to defective bronchial drainage. The heart is displaced to the left and compressed which may interfere with its filling and reduce exercise tolerance. The time to correct the deformity is before it involves structures other than the sternum. The procedure recommended for infants less than sixteen months of age consists of separating the xiphoid from the sternum and allowing the diaphragm to pull it back. In a more radical operation the xiphoid and the lower part of the sternum are forcibly drawn anteriorly and maintained in position by wires fastened to an external appliance placed across the chest. After approximately five years of age, changes in the bony structures cannot be entirely corrected. Operation at any age will relieve pressure symptoms and probably give an 80 per cent correction of the deformity. In the older patients, flattening and narrowing of the chest due to the downward slant of the ribs will persist though kyphosis can be rectified by corrective exercises. There have been no deaths in the 31 cases operated upon by the author. In the discussion of this paper, A. Ochsner presented a man of 34 whose deformity was so severe that the Lexer procedure was used to turn the sternum and costal cartilages inside out; the result was satisfactory. J. E. Dailey recommended the use of a segment of the ninth rib as a bridge from the second rib on one side to the third-rib stump on the other. The sternum rests upon this bridge after resection of the parasternal cartilages. This technique was suggested for certain cases of severe crushing injury to immobilise the sternum and combat paradoxical respiration.—*Funnel chest and allied deformities of the thoracic cage, C. W. Lester, J. Thoracic Surg., April, 1950, 19: 507.—(R. E. MacQuigg)*

Reconstruction of the Anterior Thoracic Wall.—Sacrifice of large portions of the chest wall may be required in (*1*) primary neoplasms arising in the bony thoracic wall, (*2*) recurrent mammary cancer invading the bony thorax, and (*3*) primary carcinoma of the breast invading the thoracic wall near the costal cartilages where protection is not afforded by interposition of the pectoral muscles. Repair can be effected by utilizing (*1*) a fascia lata graft to replace the pleural defect, (*2*) complete

mobilization and transplantation of the latissimus dorsi with preservation of its blood and nerve supply, and (3) coverage with split-thickness skin grafts.—*Reconstruction of the anterior thoracic wall, D. A. Campbell, J. Thoracic Surg., March, 1950, 19: 456.*—(*R. E. MacQuigg*)

Tantalum Plate for Chest Wall.—The resection of large areas of the chest wall which are the seat of malignant disease has a much wider application at the present time than was heretofore possible. Cancer of the lung with extension to pleura and ribs has in the past been considered inoperable. This concept is being revised in the light of present knowledge that the peripheral lesions have a tendency to local invasion, rather than to early spread to the mediastinum, as is the case with those more centrally located. Hope is offered to a relatively large group of patients formerly considered hopeless. Three cases illustrate solutions to the problem of the flabby chest wall by insertion of tantalum plates with large lateral pedicle flaps as indicated. This not only overcomes postoperative hazards but gives stability and improves final function.—*The use of tantalum plate when resecting large areas of the chest wall, J. M. Beardsley, J. Thoracic Surg., March, 1950, 19: 444.*—(*R. E. MacQuigg*)

Esophageal Motility in Mega-esophagus.—Fluoroscopy and ballon kymography were used to study 2 patients with achalasia of the esophagus treated by esophagogastrostomy and 3 normal persons. Normally there are frequent organized contractions related to effective peristalsis. In achalasia these movements were uncoordinated or absent so that the esophagus never appreciably emptied of its barium when the patient was in the Trendelenburg position. Achalasia differs from true esophagospasm in which hypermotility may occur. Disturbed peristalsis or even total paralysis of the esophagus may be present in achalasia explaining the failure of the esophagus to return to normal size after adequate esophagogastrostomy. These studies also indicate that the stoma must offer the least resistance to gravitational outflow. The atropine drugs depress motility and peristalsis still further but they decrease salivation and may give symptomatic relief. A sympathicolytic drug like ergotamine and a drug which has the peripheral effects of acetylcholine, such as urecholine, are worthy of clinical trial in the conservative management of achalasia and in the postoperative treatment. Recent data contradict the earlier consensus that pain sensations in achalasia are conveyed by vagal afferent fibers and offer further evidence for the theory that achalasia causes idiopathic mega-esophagus.—*The role of esophageal motility in the surgical treatment of mega-esophagus, I. D. Puppel, J. Thoracic Surg., March, 1950, 19: 571.*—(*R. E. MacQuigg*)

Esophagotracheobronchial Fistula.—The 4 cases of esophagotracheobronchial fistula reported here were under observation for ten months to eight years without correctly being recognized although characteristic symptoms invariably develop. Ingestion of fluids is followed by strangling or severe coughing after a momentary pause; chronic cough and repeated pneumonias are common. Ingestion of iodized oil is preferable to the use of barium for diagnosis as it is less irritating to the tracheobronchial tree. Approximately one-half of the acquired communications are caused by malignancy; trauma is the cause in approximately one-third. Between 1916 and 1949, 75 cases of nonmalignant fistulas were reported. Small fistulas should receive local cauterization and antibiotics in expectation of a cure or alleviation preparatory to surgery. Fistulas complicated by bronchiectasis or lung abscess frequently require pulmonary resection in addition to closure of the esophageal defect. The 4 patients presented were successfully treated by direct surgical closure.—*Acquired nonmalignant esophagotracheobronchial fistula, F. P. Coleman & G. H. Bunch, Jr., J. Thoracic Surg., April, 1950, 19: 542.*—(*R. E. MacQuigg*)

Mitral Valvuloplasty.—While previous work has been based on the concept of exchanging regurgitation for stenosis, it does not follow that this is either desirable or necessary. At present there is no method for measuring the degree of regurgitation or of stenosis in a patient. High-grade mitral stenosis can exist in patients whose resting cardiac output is normal as determined by catheterization. Definite clinical improvement may take place following valvuloplasty with significant lowering of the pulmonary artery pressure but with no change in resting cardiac output. The surgical principles are: (*1*) The heart should not be dislocated during the operation. (*2*) The stenotic valve should be approached from the auricular side so that the funnel directs the instrument toward the leaflet margin. (*3*) Surgical enlargement should give minimal regurgitation and maximal restoration of valvular function. This is properly a valvuloplasty. (*4*) In the presence of mitral obstruction or regurgitation, undue acceleration of heart rate must be avoided by adequate digitalization and the use of intravenous procaine. Tachycardia increases the pulmonary vascular pressure. (*5*) Blind maneuvers must be well controlled and deliberate. (*6*) There must be minimal stimulation of the ventricular endocardium. A new operating tunnel provides opportunity for a more deliberate, better controlled operation. Valvuloplasty was performed in 5 patients; 3 died.—*The surgical treatment of mitral stenosis: II. Progress in developing a controlled valvuloplastic technique, D. E. Harken, L. B. Ellis, & L. R. Norman, J. Thoracic Surg., January, 1950, 19: 1.*—(*R. E. MacQuigg*)

Surgery of Mitral Stenosis.—Possible surgical approaches to mitral stenosis are (*1*) bypassing the stenotic mitral valve, (*2*) relieving the associated pulmonary hypertension, or (*3*) direct surgical attack on the valve. No useful method is known for the first approach. For relief of pulmonary hypertension, the azygos and pulmonary veins have been anastamosed and septal defects have been created. In effect, this produces a Lutembacher's syndrome which is little better than uncomplicated mitral stenosis. The first section of the mitral ring was by Cutler in 1923. Simple incision of a cusp usually leads to fatal regurgitation and excision of part of the valve ring is poorly tolerated. Digital dilatation of the stenotic valve has had occasional success but is believed to be unsound. Commissurotomy restores a marked degree of normal function. It is performed by passing a purse string suture around the auricular appendage, amputating its tip and exploring the valve with the index finger; a special knife introduced along the finger divides the anterolateral commissure. A narrow-bladed commissurotomy punch is used for very hard valves. Ambulation is permitted in two to five days. In 4 of 7 patients, this method was successful and in them no regurgitation was produced. Preoperative studies should be complete; cardiac catheterization provides the best objective evaluation of the results. The most favorable candidates are patients with excessive fatigability, normal sinus rhythm, a predominantly stenotic lesion, and evidence of pulmonary hypertension. Contraindications are active rheumatic disease, subacute bacterial endocarditis, uncontrollable cardiac failure, and marked associated regurgitation or other valvular deformities.—*The surgery of mitral stenosis, C. P. Bailey, R. P. Glover, & T. J. E. O'Neill, J. Thoracic Surg., January, 1950, 19: 16.*— (*R. E. MacQuigg*)

Pulmonary Alveolar Adenomatosis.—A patient developed pulmonary symptoms shortly after casual exposure to a flock of sick sheep. Lobectomy revealed alveolar adenomatosis or alveolar cell carcinoma of the lung. Recurrence was found roentgenographically seven months later. Graham stated in discussing the paper that this disease is multicentric and cure cannot be expected by excision. At the time jagziekte was investigated in sheep by Cowdry it was known only in South Africa. Now it has spread around the world and has involved sheep in the United States. The disease is in many respects like mouse lung cancer which is really multiple malignant adenomatosis and

has been thought to be due to genetic factors. There are reasons for thinking this condition is similar to jagziekte. A virus infection may be responsible for both. O. T. Clagett stated that 5 per cent of the cases of carcinoma of the lung at autopsy were of this type.—*Pulmonary alveolar adenomatosis, H. B. Stevens & S. J. Shipman, J. Thoracic Surg., April, 1950, 19: 589.—(R. E. MacQuigg)*

ANTIMICROBIAL THERAPY

Tuberculous Meningitis.—Streptomycin has been used to treat 93 patients with tuberculous meningitis. The first 60 of these patients began treatment more than a year ago; 50 per cent recovered. Four of the 60 patients relapsed after a full course of therapy. Of the first 60 patients, 5 became totally deaf. Total deafness should not be regarded as a contraindication for continuation of treatment with streptomycin except in children who have not yet learned to talk. Seriously streptomycin-resistant bacilli appeared in the cerebrospinal fluid of 6 of the first 80 patients. The treatment consisted of streptomycin intrathecally, 100 mg. for adults and 50 to 75 mg. for infants and children, daily for the first six to twelve weeks or longer, with streptomycin intramuscularly, 2 gm. for adults and 20 mg. per pound of body weight for infants and children, daily for not less than six months. This was followed by sanatorium treatment for a further three to six months. When meningitis was associated with miliary tuberculosis, the results were bad and streptomycin, therefore, was given intramuscularly daily for twelve months with three or four courses of streptomycin intrathecally during the same period. The results justified the prolonged treatment. There has been a tendency also to prolong therapy even for patients with meningitis not associated with miliary tuberculosis. If the subarachnoidal space became blocked, bifrontal burr holes were immediately made and streptomycin was injected into the ventricles or into the cisterna magna. It may be best to make frontal burr holes in all cases at the outset of treatment. After intrathecal injections, nystagmus, vertigo, nausea, and vomiting are common. They usually stop when the meningitis is controlled even though streptomycin is still given. In the first months of daily intrathecal injections, there is often a meningeal reaction which should not be regarded as a toxic symptom but as evidence of a process which is essential to recovery. There is fever, head retraction, spinal rigidity, and an increase of cells and protein in the cerebrospinal fluid. A sharp rise in cells and protein appears to be specific for tuberculous meningitis and might be caused by the liberation of tuberculin. Purified protein derivative was injected intrathecally, therefore, in 3 patients for whom all hope of recovery had been abandoned. Two patients recovered, the third died. Necropsy showed that the meningitis had largely resolved, but there was a tuberculoma in the temporal lobe. The intrathecal use of tuberculin seems to result in a lysis of the exudate. The reaction is alarmingly severe and tuberculin should be used in carefully graded doses. If the Mantoux test is strongly positive, the initial dose is 0.0000035 mg. of purified protein derivative. Injections are given every other day, doubling the preceding dose each time until a reaction is obtained. Once there is a clinical or meningeal reaction the injections are usually given every four days, the dosage and its rate of increase being adjusted to the intensity of reaction. If the Mantoux reaction is weakly positive, the initial dose of tuberculin is 0.0000075 mg. and the dose is trebled or quadrupled every other day. This treatment is continued until the clinical recovery is beyond question. The dosage and length of treatment with streptomycin is not altered by the addition of the tuberculin treatment.—*Tuberculous meningitis, H. Cairns, H. V. Smith, & R. L. Vollum, J.A.M.A., September 9, 1950, 144: 92.—(H. Abeles)*

Organic Acids and Tubercle Bacilli.—Active tuberculous lesions, especially caseous "closed" areas, contain surprisingly few acid-fast organisms. It seems probable that inflammation and necrosis produce an environment unfavorable to tubercle bacilli. It appears

unlikely that oxygen deprivation can be the sole direct cause for the disappearance of bacteria from "closed" lesions, for some oxygen must diffuse into the aqueous phase of the caseous material. Areas of inflammation and caseation can become acidic and reach a pH of 6.5, but it is unlikely that the hydrogen ion concentration in a tuberculous lesion ever becomes toxic for acid-fast bacilli since their optimal *in vitro* range is between pH 6.2 and 6.8. In inflammatory and caseous areas there is accumulation of metabolic constituents and of autolytic products from tissue cells. The effect on tubercle bacilli of some of the organic acids produced during cellular metabolism or by autolysis was studied in many strains of tubercle bacilli; the results obtained with fully virulent human H37Rv and Ravenel bovine strains are reported. Bacillary growth was inhibited *in vitro* by adding low concentrations of the sodium salts of some organic acids to liquid and agar media containing whole serum or serum albumins. The short-chain aliphatic acids such as acetic, propionic, butyric, caproic, caprylic, and capric acids exerted a marked inhibitory effect on the growth. Capric acid was the most active of the substances tested. Inhibition of growth could also be demonstrated readily with low concentrations of lactic acid but not with keto and dicarboxylic acids. The inhibitory activity of the aliphatic acids and of lactic acid increased as the pH of the medium was lowered. The inhibitory effect appears to be bacteriostatic rather than bactericidal and to depend upon a disturbance of the normal metabolic processes of the bacilli. In contradistinction adequate concentrations of some long-chain fatty acids, oleic and lignoceric in particular, markedly increased growth in media containing enough serum albumin to overcome their toxicity. The organic acids in inflammatory and caseous areas constitutes only one of the several factors which may affect the course of tuberculous infection. Tubercle bacilli are readily phagocytised and there is evidence that the ability of the infected host to overcome infection ultimately depends upon the power of the monocytes to kill engulfed bacilli.—*The effect of organic acids on mammalian tubercle bacilli, R. J. Dubos, J. Exper. Med., October 1, 1950, 92: 319.*—(*J. S. Woolley*)

Evaluation of Antituberculosis Agents.—The authors inoculated intravenously 30 three-week-old chickens with 0.01 mg. of *Mycobacterium tuberculosis avium*. The animals were divided into five groups of 6 chickens each: (*1*) The culture controls were sacrificed three weeks after inoculation. (*2*) Streptomycin, 40 mg. per kg. of body weight, was given subcutaneously in two equal doses. (*3*) p-Aminosalicylic acid (PAS), 1 gm. per kg. of body weight, as the sodium salt was introduced into the crop daily in a single dose. (*4*) Both streptomycin and sodium PAS were given in the dosages used in groups (*2*) and (*3*). (*5*) No drugs were given to the untreated controls. Two chickens of the latter group died from tuberculosis approximately eight weeks after infection. None of the treated animals died from tuberculosis. Nine weeks after inoculation, all animals were sacrificed and autopsied. From this experiment it seems that streptomycin has marked activity against established avian tuberculosis in the chick; the effect of sodium PAS is slight.—*The use of chicks in the evaluation of antituberculosis agents, J. Carmichael & M. H. Maclay, J. Path. & Bact., July, 1950, 62: 363.*—(*H. G. Henderson*)

Treatment of BCG Abscesses.—Following BCG vaccinations there are occasionally large and prolonged ulcerations. Treatment of these with a 20 per cent para-aminosalicylic acid ointment has been effective. The treatment is begun after the tuberculin reaction has become positive.—*Ueber die Behandlung von lang dauernden Impfreaktionen nach BCG, A. Fischer, Wien. klin. Wchnschr., October 6, 1950, 62: 759.*—(*G. C. Leiner*)

Psittacosis.—A 32-year-old male office worker handled a broken vial of lyophilised psittacosis virus. Five days later he developed a cough and aching in his chest. Nine days after the exposure to the psittacosis virus he

was admitted to a hospital with the complaints of fever, headache, and cough. The total leukocyte count was 7,200. The complement fixation test for psittacosis was negative. A roentgenogram of the chest showed a small linear area of increased density in the base of the left lung. The patient was treated with aureomycin and became afebrile within three days. The pulmonary lesion increased initially but resolved almost completely fifteen days after the onset of the illness. The psittacosis virus was not isolated from either sputum or blood. On the twelfth day the titer of the complement fixation test for psittacosis rose to 1:40, and on the fifteenth day to 1:640. The patient was discharged twelve days after the onset of the illness.—*Aureomycin therapy of human psittacosis, T. W. Green, J.A.M.A., September 16, 1950, 144: 237.—(H. Abeles)*

LABORATORY STUDIES

Dubos Medium for Routine Cultures.—The use of liquid Dubos Tween-albumin medium for direct isolation of tubercle bacilli from pathologic material was investigated with 1,560 specimens of sputum, gastric contents, pleural and other fluids obtained from patients with tuberculosis. Warm sodium hydroxide, 4 per cent, was added in quantities equal to that of the specimen. After shaking, the treated material was centrifuged in three 15-milliliter amounts. The entire sediment from one tube was smeared for staining for bacilli. The sediments in the other tubes were neutralized and planted (*1*) in Dubos Tween-albumin medium with 10 units of penicillin per milliliter and (*2*) on the potato-egg medium of Woolley and Petrick. During incubation at 37° C., smears were made from the liquid cultures at weekly intervals for a month. On the same days, subcultures were made onto potato-egg slants. If the smear of the liquid culture showed no tubercle bacilli on the twenty-first day, it was centrifuged one week later and a subculture of the sediment made on the solid medium. The original cultures and subcultures on potato-egg slants were examined weekly for eight weeks before being called negative. Of the 1,560 specimens studied by slide or culture, 916 were positive. Of these, 737 were positive in Dubos medium, 742 grew on potato-egg slants; 105 were positive in Dubos, and negative on potato-egg medium; 90 were negative in Dubos, positive on potato-egg medium. Of the Dubos cultures, 108 were contaminated; 52 of the slants were dried or contaminated. More than 40 per cent were positive on the initial smear. Positive cultures often were detected after seven to ten days in the Dubos tubes but rarely before twenty-one days on the solid medium. It was necessary, however, to make smears of all the liquid cultures in order to recognize the acid-fast bacilli.—*The Dubos medium in routine cultivation of tubercle bacilli: Results of a comparative study with Petrik's medium, M. Mollov, I. Hill, & A. Oshinsky, Am. J. Clin. Path., November, 1950, 20: 1085.—(J. S. Woolley)*

Vitamin C and Tubercle Bacilli.—In order to determine the effect of vitamin C on cultures of tubercle bacilli, ascorbic acid neutralized with sodium bicarbonate was added to media. Homogeneous, virulent cultures of 3 strains of tubercle bacilli were employed. Vitamen C was found to have a bactericidal effect on such cultures at concentrations of 1:200 and higher when the tubes contained 20 million organisms, at 1:500 for 500,000 organisms, and at 1:1,000 for 25,000 organisms. A retarding effect was noted in dilutions of 1:2,000, 1:5,000, and 1:10,000. For virulent bacilli on Youmans' medium, ascorbic acid was bactericidal in concentrations of 1:1,000 and higher. Tubercle bacilli in this medium were found to be more sensitive to vitamin C than bacilli in homogeneous culture. No bactericidal effect was found with other organisms; a slight retarding effect was observed with *Staphylococci* at high concentrations of vitamin C. —*Action bactéricide pour le bacille de Koch de la vitamine C à doses élevées. Comparaison avec son action sur un certain nombre d'autres microbes, P. Pichat & A. Revilleau, Ann. Inst. Pasteur, September, 1950, 79: 342.—(V. Leiles)*

Vitamin K and Tubercle Bacilli.—The *in vitro* tuberculostatic effect of 3 analogs of vitamin K, 4-amino-2-methyl-1-naphthol hydrochloride ("synkamin"), 2-methyl-1,4-naphthoquinone sodium bisulfite ("hykinone"), and tetrasodium 2-methyl-1,4-naphthoquinone diphosphoric acid ester ("synkayvite" or "kappadione") were studied. The critical concentration for "synkamin" was 1 γ per ml.; for "hykinone", 2 γ per ml., and for "synkayvite" or "kappadione", 100 γ per ml. (Author's summary). —*The in vitro effect of analogs of vitamin K on Mycobacterium tuberculosis var. hominis strain H37Rv, A. Kimber, J. Bact., October 1950, 60: 469.*—(*F. G. Petrik*)

Acidosis during Thoracic Surgery.—The blood oxygen and carbon dioxide, the pH and hematocrit values were measured before and during anesthesia, and occasionally the day after surgery, in 43 patients receiving nitrous oxide-oxygen. The techniques employed were not adequate to remove carbon dioxide and, even though the actual carbon dioxide content does not increase, the rise in tension is effected by a serious fall in pH. This rise in turn begins shortly after the patient is placed in the lateral position and continues with increasing rapidity. Attention is called to the probable relationship between the high carbon dioxide tensions and the sudden fall of blood pressure which occasionaly is fatal at the end of operation. The rise does not occur with patients in the supine position.—*Acidosis during thoracic surgery, H. K. Beecher & A. J., Murphy, J. Thoracic Surg., January, 1950, 19: 50.*—(*R. E. MacQuigg*)

Electrophrenic Respiration.—The immediate inhibition of spontaneous breathing during electrophrenic respiration in nembutalized dogs is favored by (*1*) increasing the rate of artificial respiration, (*2*) increasing its depth with higher voltage applied to phrenic nerve, and (*3*) increasing the duration of inspiration in any given respiratory cycle. The inhibition depends, at least in part, on afferent impulses in the vagi. Hypercapnia, which is known to increase the excitability of the respiratory center, elevates the threshold for reflex central inhibition during electrophrenic respiration. Inspiratory intercostal activity is also inhibited during electrophrenic respiration. It is concluded that the immediate suppression of spontaneous breathing during electrophrenic respiration is due to inhibitory vagal afferent impulses which prevent the spontaneous discharge of the respiratory center. In addition to the usual suppression of spontaneous respiration, reflex excitation of the inspiratory center can be achieved by producing an excessive diaphragmatic contraction. Producing an active descent of one leaf of the diaphragm by stimulation of a phrenic nerve seems to be a more effective stimulus for inhibition of spontaneous respiration than inflation of the lungs by positive pressure. This would suggest the operation of factors other than those concerned solely with simple distention of the pulmonary parenchyma. Prolonging the duration of inspiration in any one cycle should more effectively inhibit spontaneous respiration while not affecting ventilation to any great extent (Authors' summary).—*Role of pulmonary proprioceptive reflexes in suppression of spontaneous breathing during electrophrenic respiration, P. O. Chatfield & S. J. Sarnoff, Am. J. Physiol., October 1, 1950, 163: 118.*—(*G. C. Leiner*)

Artificial Aortic Valve.—Valves made of methyl methacrylate and placed within the aorta distal to lacerated aortic leaflets in dogs have functioned as satisfactory correction of regurgitation up to seven days of observation. Ultimate survival was being studied at the time of this report. In 1937, Hufnagel showed that a cylinder of this material could replace an excised segment of canine aorta and that, when several animals were sacrificed after six months, there was little tissue reaction at the junction. No mural thrombi were present.—*An artificial aortic valve, J. M. Campbell, J. Thoracic Surg., February, 1950, 19: 312.*—(*R. E. MacQuigg*)

Esophageal Blood and Nerve Supply.—Mobilization of the esophagus was performed in

63 dogs. The blood supply was sufficiently rich to allow the cervical or the thoracic esophagus to be freed through the diaphragm; when both cervical and thoracic portions were mobilized, perforation or stricture occurred in nearly one-half of the animals. The more extensively the esophageal fibers of the vagus were disturbed near the diaphragm, the more marked was the resultant cardiospasm. Denervation of the esophagus caused loss of peristalsis followed by complete recovery from six to sixteen weeks after operation. The esophageal tissue of man and the dog is sufficiently similar in texture and consistency for surgical comparison.—*Blood and nerve supply to the esophagus, O. Swenson, K. Merrill, Jr., E. C. Peirce II, & H. F. Rheinlander, J. Thoracic Surg., March, 1950, 19: 462.*—(*R. E. MacQuigg*)

Blood Supply of the Esophagus.—In 32 dogs, varying lengths of the esophagus were resected and the remainder was deprived of a part of its blood supply. In each instance, end-to-end anastomosis was successful. Arteriograms showed that the right gastric artery can supply the esophagus as high as its cervical segment even though all the other arteries are severed. In the discussion of the paper, Sweet pointed out that in local resection of the relatively rare benign localised strictures there often is recurrence of the causative esophagitis near the anastomotic site. In carcinoma, early recurrence detracts from the value of a palliative operation of such magnitude. Tuttle stated that benign strictures arise as congenital web-like diaphragms in children and that it is only in the strictures arising as esophagitis that fairly wide resection should be used.—*An experimental study of the blood supply of the esophagus and its relation to esophageal resection and anastomoses, J. L. Shek, C. A. Prietto, W. M. Tuttle, & E. J. O'Brien, J. Thoracic Surg., April, 1950, 19: 523.*—(*R. E. MacQuigg*)

Transpleural Muscles.—During a student's dissection of a 60-year-old Negro, two muscles were found running up the oblique fissure of the right lung from the sixth rib posteriorly to the central tendon of the diaphragm. The nerve supply had been stripped away in the dissection, but stained sections showed a preponderance of nerves in the lower portion of the muscles, suggesting that the nerve supply was phrenic. No associated anomalies were found. Similar anomalies have not been reported previously, perhaps because such a structure might be taken for an adhesion.—*Transpleural muscles, L. Allen, J. Thoracic Surg., February, 1950, 19: 290.*—(*R. E. MacQuigg*)

PUBLIC HEALTH AND EPIDEMIOLOGY

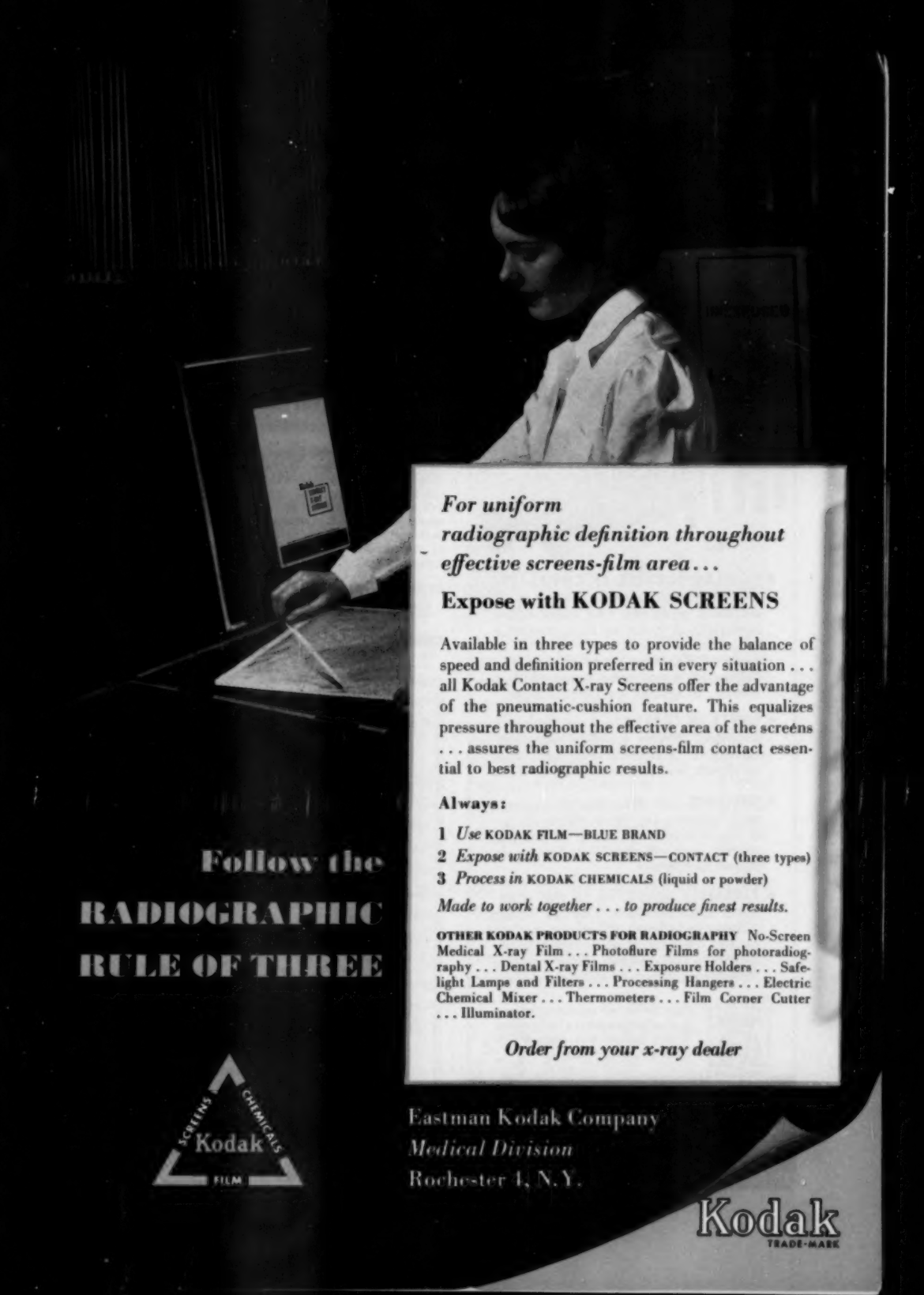
Bovine Tuberculosis in a Human Family.—Bovine tubercle bacilli were cultured from the gastric contents of a child with pulmonary tuberculosis. She had never consumed unpasteurized milk. A paternal grandmother to whom she was exposed also was found to have pulmonary tuberculosis caused by the bovine organism. It was learned that the paternal grandfather and his two brothers had all died of tuberculosis. Their father (the child's great-grandfather) had also died of the disease and had worked in an abattoir. The child's parents were found to have normal chest roentgenograms. Two years later the father developed tuberculosis due to the human bacillus. The sequence of events was believed to be as follows: The child was probably infected by her grandmother who had been infected by her husband who had been infected by his father who acquired the infection while working in the abattoir.—*Coincident bovine and human tuberculosis in a family, R. M. Todd & W. D. Gray, Tubercle, October, 1950, 31: 234.*—(*A. G. Cohen*)

Tuberculosis in Dutch Livestock.—The Chief Veterinary Inspector for Public Health in the Netherlands states that in 1949 there was a slight increase over 1948 in the percentage of slaughtered beef cattle found to be tuberculous. The respective figures were 17.2 per cent in 1949, 16.9 per cent in 1948. This is a continuation of an upward trend first ob-

served in 1947. There was a decrease of tuberculosis in swine, the corresponding figures being 2.2 per cent in 1949, and 2.6 per cent in 1948. Goats also showed a decrease from 0.4 per cent in 1948 to 0.3 per cent in 1949.—*Verslag van de Veterinair Hoofdinspecteur van de Volksgezondheid, belast met het toezicht op de naleving van de Vleeskeuringswet, Staatsblad 1919, No 524 over het jaar 1949, Verslagen en Mededelingen Betreffende de Volksgezondheid, October, 1950, 10: 769.*—(*J. van der Vate*)

Carcinoma in Chromate Workers.—A survey of the medical literature indicated that cancer of the respiratory tract has occurred in approximately 109 men employed in the chromate-producing industry and in at least 11 men employed in the chrome pigment industry. Practically all of the cases were reported in Germany and in the United States. No morbidity or mortality rates were available for the German cases, but statistical studies in this country indicated that the rates for cancer of the respiratory tract were significantly higher in the chromate-producing industry than would be expected on the basis of comparable groups not exposed to chromates. There were no data to indicate that persons exposed to chromates in other occupations were more than normally liable to cancer of the respiratory tract or that the incidence of cancer in other tissues was excessively high in chromate workers. The majority of the cancers in these chromate workers were bronchogenic carcinomas, although a few were located in the upper respiratory tract. In clinical symptoms and pathological changes these cases did not differ in any characteristic manner from other cases of lung cancer. The lung cancer cases in the chromate workers of the United States showed a younger age distribution than is normally found for lung cancer cases among men in this country. Some cancers occurred in men who had been exposed to chromates only four years but the majority did not appear until after many years of exposure. In most cases reported in the literature, the onset of illness occurred while the men were still employed at the chromate plant but in some cases a number of years elapsed between the termination of employment and the onset of illness. The concentration of chromates in the atmosphere of the plants where these men had worked was not known. Since the majority worked in old plants they were probably exposed to high concentrations of chromates. The materials which were suggested as responsible for this carcinogenic effect were the hexavalent chromium compounds in the form of dust, particularly the sodium and potassium monochromates or dichromates and zinc chromate. The mechanism of action is not known. Adequate laboratory experiments on this problem are lacking at present (Author's summary).—*Pulmonary carcinoma in chromate workers: I. A. review of the literature and report of cases, A. M. Baetjer, Arch. Indust. Hyg. & Occup. Med., November, 1950, 2: 487.* (*T. H. Noehren*)

Heart Disease in Survey Radiography.—In two surveys using miniature films, 12,173 patients were roentgenographed; 47 cases of cardiac disease were diagnosed radiographically and confirmed by clinical examination. Of these, 19 cases had not been previously diagnosed and would probably benefit from medical supervision. The majority of the cases were either rheumatic or hypertensive heart disease although there were 8 cases of congenital heart disease, 7 of which had been previously diagnosed clinically. The patients were asymptomatic including 2 with interventricular septal defects, 4 patients with interauricular septal defects, and 2 patients with dextrocardia and situs inversus. It is considered that such surveys are of value in identifying some cases of cardiac disease although a large number may be missed.—*Cardiological case finding by means of mass miniature radiography, P. O. Leggat, Brit. M. J., December 16, 1950, No. 4693: 1384.*—(*E. A. Riley*)



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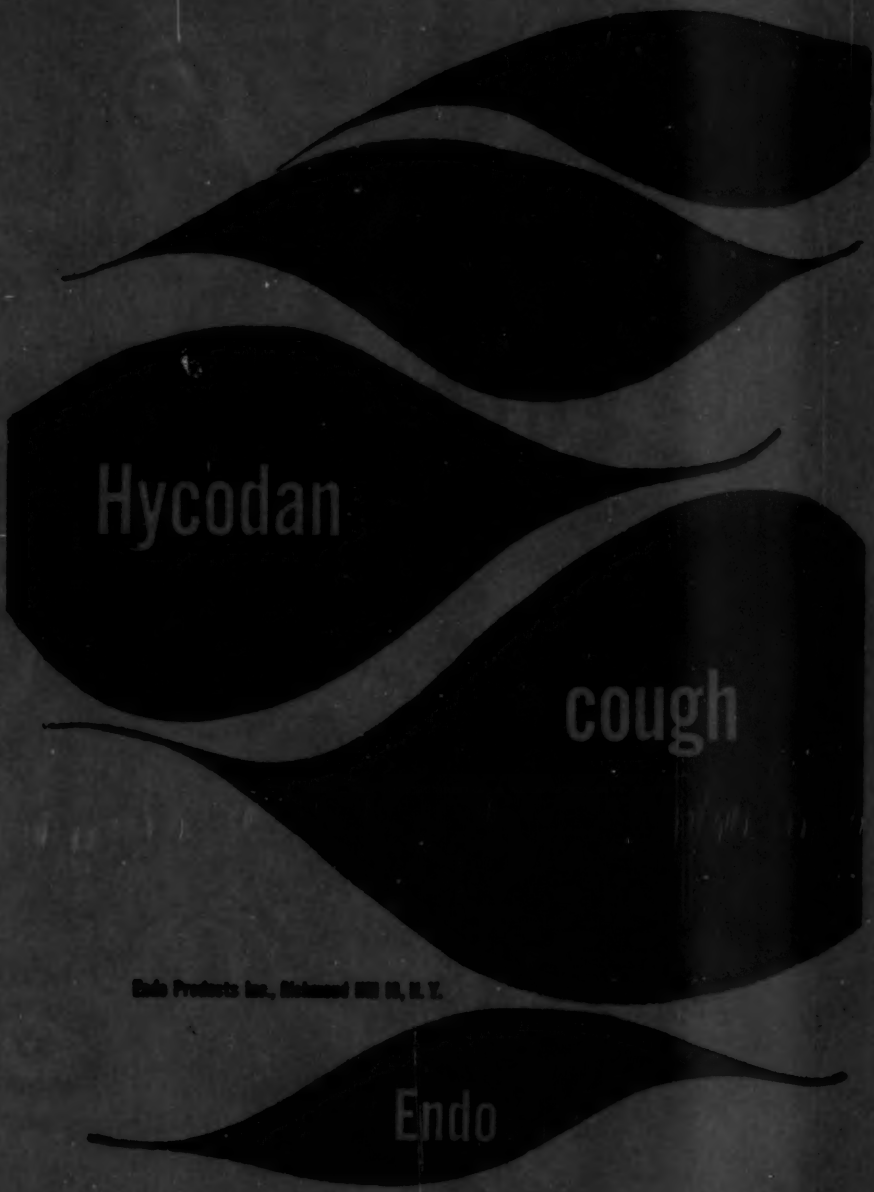

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